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Cellular Therapy and Follicular Lymphoma: Where Do We Stand in 2025?

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Introduction

Patients with low-risk follicular lymphoma (FL) have a median overall survival (OS) exceeding 20 years.[1] Whereas those with adverse features, such as a high Follicular Lymphoma International Prognostic Index (FLIPI) score or progression of disease within 24 months of front-line treatment (POD24) have inferior outcomes.[1] Standardized treatment in the second line and beyond is not firmly established and largely depends on patient fitness and medication access. The duration of response decreases with each line of therapy.[2] In this review, we evaluate the evidence for T-cell-redirecting therapies in FL.

Chimeric Antigen Receptor T cell (CAR T) Therapy in FL

CAR T-cell therapy involves the modification of donor T-cells to induce the expression of chimeric antigen receptors (CARs), which are highly specified receptors that target specific antigens. CAR T-cell therapy can cause direct cellular toxicity to antigen-positive cells, while it also may recruit other components of the immune system, resulting in highly targeted anti-tumour effects. The persistence of CAR T-cells with a memory-like phenotype can result in long-term disease control years after the administration of this living drug. CAR T-cell therapy is highly effective in relapsed or refractory (r/r) FL, which has resulted in the regulatory approval of this therapy in the third-line setting. The following three autologous, second-generation CD19-targeting CAR T-cell therapies have the most mature evidence.

Axicabtagene ciloleucel (Yescarta) utilizes a CD28 co-stimulatory domain, which drives rapid T-cell expansion but results in shorter persistence. The ZUMA-5 Phase 2 trial evaluated patients with FL (n=124) or marginal zone lymphoma (n=24), and high-risk patients were well represented (**Table 1**).[3] With a median follow-up of 17.5 months, the overall response rates (ORR) and complete response (CR) rates in patients with FL were high at 94% and 79%.[3] No differences in ORR were detected in patients with POD24, prior autologous stem cell transplant (ASCT), or several lines of prior therapy.[3] Toxicity was manageable, with 18% of patients experiencing grade ≥3 immune effector cell–associated neurotoxicity syndrome (ICANS) and 6% experiencing grade ≥3 cytokine release syndrome (CRS) with one fatal event.[3] Long-term follow-up of the FL cohort showed an excellent median progression-free survival (PFS) of 40.2 months.[4]

Additional analyses revealed that patients with the lowest quartile of metabolic tumour volume (MTV) had nearly double the 36-month PFS compared to those with the highest MTV (60% vs. 33%).[4] Patients never exposed to bendamustine had the highest 36-month PFS (70%), and those exposed within 6 months had the lowest PFS (25%); however, it is likely that disease behaviour, such as early relapse, also plays into these results.[4] Interestingly, this study also showed that four patients died of drug-related adverse events (AE). It is important to note that 13 secondary primary malignancies (SPMs) were observed, including four that were fatal. None of these deaths were considered treatment-related, though SPMs are a known risk of CAR T-cell therapy and the second leading cause of non-relapse mortality.[4,5]

Tisagenlecleucel (Kymriah) utilizes a 4-1BB co-stimulatory domain, which drives more gradual T-cell expansion and prolonged persistence. The Phase 2 ELARA trial evaluated 97 patients with r/r FL after ≥2 prior therapies, which included many patients with high-risk features (**Table 1**).[6] High-risk features were prevalent; 63% of patients

Trial	ZUMA-5 (3) Phase II study	ELARA (6) Phase II study	TRANSCEND FL (9) Phase II study
Product/trade name	Axicabtagene ciloleucel/*Yescarta*	Tisagenlecleucel/*Kymriah*	Lisocabtagene maraleucel/*Breyanzi*
Number of patients	124 (FL cohort)	97	130
Median follow-up	17.5 months	16.6 months	18.9 months
Population	≥2 prior lines of therapy, including anti-CD20 mAb and alkylating agent	≥2 prior lines of therapy	≥2 prior lines of therapy (+3L) or 1 prior line (2L) with POD24 and therapy initiation <6 months from diagnosis OR high tumour burden by mGELF
High-risk features			
High tumour bulk by GELF	52%	Not reported	56%
POD24	55%	62.9%	45%
FLIPI ≥3	44%	59.8%	53%
Stage 3–4	85%	85.6%	87%
Prior ASCT	24%	36.1%	25%
ORR	94%	86%	97%
CR rate	79%	69%	94%
12-month PFS	79.1%	67%	83%
12-month OS	94.2 %	95%	93%
CRS (grade ≥3)	78% (6%)	49% (0%)	58% (1%)
Neurologic events (grade ≥3)	56% (15%)	23% (1%)	15% (2%)

Table 1. Landmark CAR-T cell therapy trials in follicular lymphoma; *courtesy of Hadel El-Haddad, MD and Hannah Cherniawsky, MD, MSc.*

Abbreviations: ASCT: autologous stem cell transplant; **CR:** complete response; **CRS:** cytokine release syndrome; **FL:** follicular lymphoma; **FLIPI:** Follicular Lymphoma International Prognostic Index; **mAb:** monoclonal antibody; **(m) GELF:** (modified) Groupe d'Etude des Lymphomes Folliculaires; **ORR:** objective response rate; **OS:** overall survival; **POD24:** progression of disease within 24 months of front-line treatment; **PFS:** progression-free survival

had POD24, 60% had FLIPI scores ≥3, and 36% had undergone prior ASCT.[6] With a median follow-up of 16.6 months, the ORR was 86%, and the CR rate was 69%.[6] Responses were similar in high-risk subgroups, including those with POD24, high tumour burden, and double-refractory disease.[6] Median PFS has not been met, even with longer follow-up data.[7] The estimated 12-month PFS and OS were 67% and 95%, respectively.[7] Grade ≥3 CRS and ICANS occurred in ≤1% of patients, and most cytopenias resolved by month 24.[6]

Exploratory analyses revealed improved outcomes in patients who, at baseline, had lower MTV, higher levels of naïve CD8+ T cells, and lower T-cell exhaustion marker expression.[7] A comparative analysis of Zuma-5 and ELARA suggested similar efficacy but lower adverse effects with tisagenlecleucel than with axicabtagene autoleucel.[8] Large-scale, comparative registry data are keenly awaited. Despite a lack of head-to-head comparison, prospective trials and similar retrospective series evaluating large B-cell lymphoma (LBCL) in the third line have significantly impacted prescribing.

Lisocabtagene maraleucel (Breyanzi) utilizes a 4-1BB co-stimulatory domain and a 1:1 CD4:CD8 ratio. The Phase 2 TRANSCEND FL trial enrolled patients to be treated in the third (3L+) or second (2L) line. Patients with high-risk features, namely POD24, systemic treatment within 6 months of diagnosis, and/or high tumour burden defined by the modified Groupe d'Etude des Lymphomes Folliculaires (GELF) criteria, were included in this study.[9]

In the 3L+ cohort (n=101), the ORR was 97%, and the CR rate was 94%.[9] The high-risk 2L cohort (n=23) also had excellent results with an ORR and CR rate of 96%.[9] At a median follow-up of 18.9 months, the median PFS was not reached, though the 12-month point estimate was 83% overall.[9] Toxicity was manageable, with grade ≥3 CRS observed in 1% and grade ≥3 neurologic events in 2% of patients.[9] One treatment-emergent death occurred due to macrophage activation syndrome.[9] Another death due to progressive multifocal leukoencephalopathy was observed after the 90-day treatment-emergent period.[9]

Bispecific Antibodies (BAbs) in FL

BAbs represent a novel immunotherapy in which an immunoglobulin (Ig) or Ig-like structure redirects cellular components of the host immune system to their target antigen. Most BAbs in the lymphoma space engage CD3 on host T cells and CD20 on lymphoma cells to promote cytotoxicity and phagocytosis of lymphomatous cells.

Mosunetuzumab is a first-in-class IgG-like CD20xCD3 BAb with the most mature evidence in FL. An ongoing Phase 1/2 study examined fixed-duration mosunetuzumab in 90 patients with r/r FL treated with ≥2 prior lines of therapy.[10] Patients with CR received 8 cycles of mosunetuzumab, whereas those with partial remission (PR) received up to 17 cycles if ongoing benefit was derived.[10] The most recent data showed that at 3 years of follow-up, a high ORR (77.8%) and CR rate (60.0%) was achieved.[11] The median PFS was 24 months, though the duration of response (DOR) has not yet been reached in patients attaining a CR, suggesting ongoing responses in patients with CR long after drug administration has stopped.[11]

Patients with POD24 also had excellent ORR (74%) and CR rates (69%).[10] Their 36-month PFS rate was nearly identical to their non-POD24 counterparts (42% vs. 44%), and the median time to the next treatment was not reached in either group.[11,12] Patients treated in the fourth line and beyond had lower ORR (73% vs. 86%), CR (55% vs. 69%), and 36-month PFS rates (36% vs. 54%).[12] Interestingly, patients aged ≥65 years had higher ORR, CR, and 36-month PFS rates than those aged <65 years in this study.[12] No treatment-related deaths were reported.[10] CRS was observed in 44% of patients, with only 2.2% being grade ≥3, and most events occurred during cycles 1–2.[10] Neurologic events were uncommon and mainly included low-grade headaches (11%), though ICANS was not explicitly reported.[10]

Early economic analyses have suggested improved cost-effectiveness with mosunetuzumab over commercial CAR T therapies.[13,14] However, these data are based on relatively newly available therapies in the US system. Mosunetuzumab is undergoing further investigations as a combination therapy in earlier lines of therapy in the CELESTIMO and MorningLyte trials.

Epcoritamab, another C20xCD3 BAb, has been evaluated in the third-line setting for FL in a Phase 2 dose expansion cohort of the

EPCORE NHL-1 trial. Key differences between this therapy and mosunetuzumab include indefinite, subcutaneous administration with a slightly different dosing frequency. Results of the pivotal cohort (n=128) show high ORR (82%) and CR rates (63%) with a rapid median time to response of 1.4 months.[15] At a median follow-up of 17.4 months, patients with CR had not reached median PFS; however, those attaining a PR had a median PFS of <6 months.[15] Measurable residual disease (MRD) data was collected in 91 (71%) patients, of whom 61 (67%) were MRD-negative. PFS was significantly higher in patients who were MRD-negative, even across high-risk subgroups.[15] This, in turn, leads to the question about potential therapy de-escalation in MRD-negative individuals.

In the pivotal cohort, CRS was observed in 66% of patients with 2 cases of grade 3 CRS (2%).[15] ICANS (as opposed to general neurotoxicity) was reported in 6% of patients with a 2% overall risk of grade ≥3 ICANS.[15] In the optimization cohort (n=86), which utilized prophylactic steroids during cycle 1 (n=86), no grade ≥3 CRS or ICANS was observed, though 49% of patients still had grade 1–2 CRS.[15]

Glofitamab is another CD3xCD20 IgG1 BAb with an additional CD20-binding moiety, creating a 2:1 lymphoma-to-T-cell binding ratio. Glofitamab has been extensively studied in aggressive lymphoma as mono or combination therapy with monoclonal antibodies, antibody-drug conjugates, or even CAR T-cell therapy. However, data in the FL space is less mature.

A small trial evaluated step-up dosing (SUD) of glofitamab with or without obinutuzumab.[16] In the combination treatment cohort (n=19), the ORR was impressive at 100%, with a CR rate of 74%.[16] In the monotherapy cohort (n=53), the ORR was 81%, with a CR rate between 67–72% across the tested dosing schemas.[16] CRS was the most common AE, occurring in 66% of patients receiving monotherapy and in 79% of those receiving combination therapy, with only one instance of grade 3 CRS across all patients.[16] Roughly one-third of patients across both cohorts had grade 1–2 AEs, and there were no ICANS-like events.[16] Investigation of glofitamab is ongoing in various lines of therapy, combinations, and histologies, including after CAR T-cell therapy failure.[17]

CAR T vs. BAbs

Both CAR T and BAbs can result in deep and durable responses in patients with r/r FL, which has capsized the paradigm of diminishing returns with later lines of lymphoma therapy. However, both therapies have advantages and shortcomings.

While CAR T requires a single administration, autologous products come with a built-in delay due to manufacturing and the additional effort of collecting, transporting, and cryopreserving cellular material. BAbs are an “off the shelf” product that can be started quickly without risk of manufacturing failure. However, they require multiple and, in some cases, indefinite administration. CAR T is associated with higher rates of CRS and ICANS than BAbs. However, given that CAR T-cell therapy is often restricted to accredited centres, there is often greater expertise in managing severe or refractory cases. Conversely, step-up dosing used with BAbs makes their safety profile favourable; however, ongoing administration is required, which can be taxing to the patient and hospital resources.

Neither CAR T-cell therapy nor BAbs appear to be curative in FL. Both rely heavily on T-cell fitness and antigen persistence on target cells. Thus T-cell exhaustion and antigen loss can lead to relapse with either modality. Additionally, both have the on-target-off-tumour effects of B-cell aplasia, which can increase the risk of infection. However, this is more pronounced post-CAR T-cell therapy.

Future Directions

Therapy sequencing is a critical question for r/r FL, as many patients will encounter both BAbs and CAR T on their therapeutic journey. Literature in the LBCL space has demonstrated comparable results with CAR T-cell therapy between those who did not previously receive CD20 BAbs and those who did.[18] Many patients in pivotal CAR T trials are BAbs-exposed and vice versa. The Bicar study examining the use of glofitamab in r/r non-Hodgkin Lymphoma (NHL) seeks to address this in a prospective manner.[17] In patients with LBCL long-term curability of CAR T-cell therapy has made if a preferred choice to BAbs.[19] However, the relevance of this is uncertain, as more and more patients are treated in the second line. The same evidence is not yet available for r/r FL but is keenly awaited.

Optimal supportive care, such as infection prophylaxis, remains a major question in the cellular therapy field. Looking further ahead, bicistronic CAR T-cells (containing two CARs targeting different antigens), novel targets, and NK cell redirecting therapy are all in various states of investigation. Only time will tell what our armamentariums of cellular therapies will look like in the future.

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Front-line Treatment for Chronic Lymphocytic Leukemia in 2025: Finite Duration Versus Continuous Treatment

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Introduction

Chronic lymphocytic leukemia (CLL) is an indolent lymphoproliferative disorder and is the most common hematologic malignancy in Western populations. In Canada, an estimated 2,000 or more new cases are diagnosed each year.[1] Improvements in diagnostic techniques, enhanced prognostication methods, and the development of targeted treatments have revolutionized the management of CLL over the past decade. Despite an ever-expanding therapeutic landscape (**Figure 1**), the decision to initiate treatment continues to be guided by the International Workshop on CLL criteria.[2]

For patients who require treatment, we now have a choice of two treatment approaches based on current Health Canada approvals: fixed-duration therapy (e.g., chemoimmunotherapy, venetoclax-obinutuzumab [VO], or ibrutinib-venetoclax [IV]) versus continuous treatment until disease progression or toxicity (i.e., Bruton's tyrosine kinase inhibitors [BTKi]). In this review, we will summarize the evidence for these two approaches and provide our views on factors that may influence treatment selection.

Prognostic Factors in the Front-line Setting

The pioneering Rai[3] and Binet[4] staging systems utilize easily accessible clinical and laboratory parameters and have previously predicted overall survival (OS). However, these systems were developed in the chemotherapy era and are no longer used for prognostication. In the modern era, biomarkers such as b2-microglobulin, immunoglobulin heavy chain (*IGHV*) gene mutational status, and the presence of del(17p) and/or *TP53* mutations are well-established prognostic factors.[2,5] These three factors, together with age and clinical stage, have since been combined to form the CLL International Prognostic Index (CLL-IPI), which has been validated in various cohorts with moderate predictive capability in the modern era.[6,7] In the era of targeted therapies such as VO, other cytogenetic prognostic markers, such as del(13q), trisomy 12, del(11q), and even complex karyotype do not appear to have a significant prognostic impact.[8-11]

In the Canadian clinical landscape, next-generation sequencing for recurrently mutated genes in CLL other than *TP53* (e.g., *NOTCH1, SF3B1, ATM*) is not yet widely available. Currently, we lack sufficient data to recommend differing treatment approaches for patients with CLL-related mutations outside of *TP53*.

Deciphering Evidence That May Influence Treatment Choice

When considering treatment choice, it is important to thoughtfully consider the following questions and discuss them with the patient: **1)** is the convenience of an oral BTKi worth the toxicity and costs?; **2)** is the chance of cure for patients with favourable prognostic factors worth the risk of therapy-related myeloid neoplasms (tMN); **3)** is the inconvenience of ramp-up and the risk of B cell depletion during the post-pandemic era worth the treatment-free interval with VO?; **4)** is the convenience of two oral drugs worth the cardiac toxicities, particularly with ibrutinib-venetoclax?; and **5)** what is the best approach for high-risk patients?

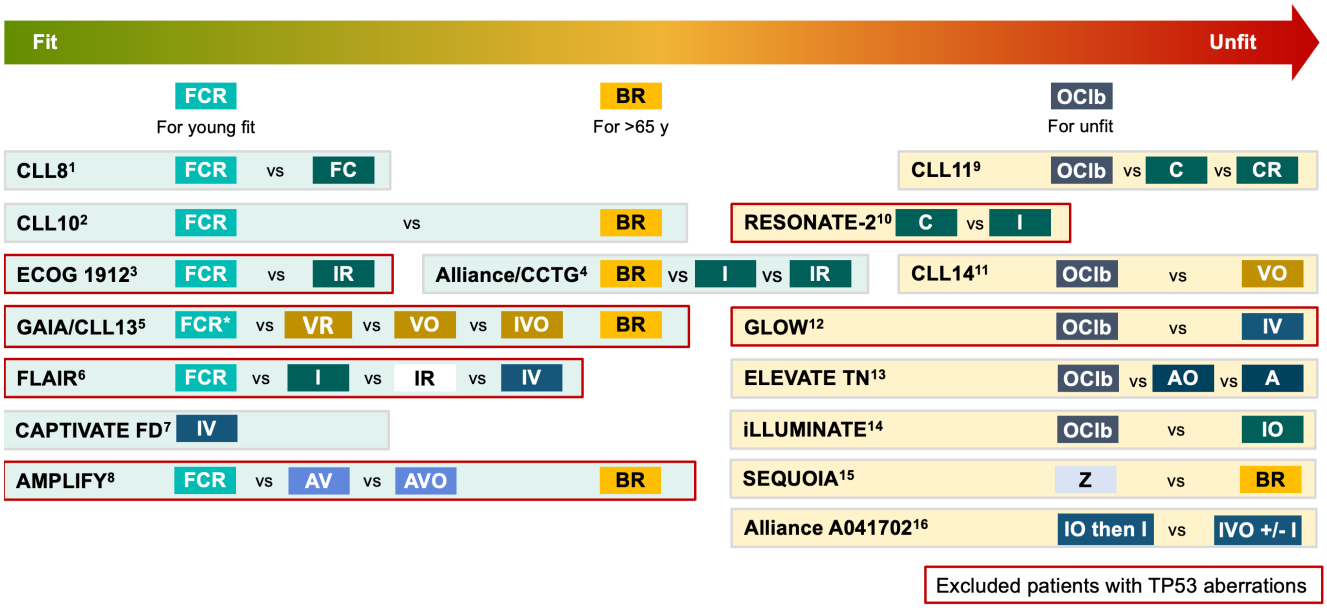


Figure 1. Published front-line treatment approaches for chronic lymphocytic leukemia; *adapted with permission from Dr. Al-Sawaf.*

[1]NCT00281918; [2]NCT00769522; [3]NCT02048813; [4]NCT01886872; [5]NCT02950051; [6]EudraCT number 2013-001944-76; [7]*non-randomized NCT02910583, [8]NCT03836261; [9]NCT01010061; [10]NCT01722487; [11]NCT02242942; [12]NCT03462719; [13]NCT02475681; [14]NCT02264574; [15]NCT03336333, [16]NCT03737981

Abbreviations: A: acalabrutinib; **AO:** acalabrutinib, obinutuzumab; **AV:** acalabrutinib, venetoclax; **AVO:** acalabrutinib, venetoclax, obinutuzumab; **BR:** bendamustine, rituximab; **C:** chlorambucil; **CR :** chlorambucil, rituximab; **FC:** fludarabine, cyclophosphamide; **FCR:** fludarabine, cyclophosphamide, rituximab; **I:** ibrutinib; **IO:** ibrutinib, obinutuzumab; **IR:** ibrutinib, rituximab; **IV:** ibrutinib, venetoclax; **IVO:** ibrutinib, venetoclax, obinutuzumab; **OClb:** obinutuzumab, chlorambucil; **VO:** venetoclax, obinutuzumab; **VR:** venetoclax, rituximab; **Z:** zanubrutinib.

BTKi: Balancing Convenience and Efficacy with Toxicity and Financial Impact

Ibrutinib is a first-generation BTKi, and its efficacy has been demonstrated in both older and younger patients with newly diagnosed CLL. Ten-year extended follow-up of the Phase 3 RESONATE-2 study of older patients (>65 years) confirmed sustained benefit of ibrutinib with a median progression-free survival (PFS) of 8.9 years (95% confidence interval [CI]: 7- not estimable [NE]).[12] Similar excellent efficacy was shown in the E1912 trial in young, fit patients.[13] Remarkably, patients treated with front-line ibrutinib have been shown to have similar OS as age-matched controls.[14]

However, the enthusiasm for BTKi is tempered by its risks. Despite the convenience of an oral treatment option, a significant discontinuation rate of both first- and second-generation BTKi has been noted in clinical trials and real-world evidence, predominantly due to arthralgia, rash, atrial fibrillation (AF), and infection.[15,16] A Canadian population-based cohort study found a high cumulative incidence of serious atrial fibrillation, bleeding, and heart failure in patients on ibrutinib compared to non-ibrutinib-treated CLL controls.[17] Similar risks have been confirmed in other analyses.[18,19] Although there are currently no head-to-head studies comparing first-generation versus second-generation BTKi in the front-line setting, the ELEVATE-RR and ALPINE studies comparing acalabrutinib or zanubrutinib to ibrutinib in the relapsed/refractory setting have demonstrated improved safety of these agents over ibrutinib, hence, second-generation BTKi are preferred over ibrutinib.[20,21] Notably, however, all BTKis are

associated with cardiac risks, including sudden cardiac death, with a black box warning about this risk in 1% of ibrutinib-treated patients.[22] Ventricular arrhythmias and sudden deaths have also been reported with both acalabrutinib and zanubrutinib.[23,24]

From a health economic perspective, continuous BTKi treatment has an associated greater all-cause monthly healthcare cost and CLL-related ongoing costs after the first 12 months of commencing treatment when compared to front-line VO.[25]

FCR: Balancing Potential for a Cure Against the Risk of tMN

Six cycles of FCR (fludarabine, cyclophosphamide, and rituximab) was historically the standard front-line treatment in fit patients based on its superior efficacy demonstrated by the CLL8 and CLL10 trials, in which patients with mutated-IGHV (M-IGHV) were shown to derive the greatest benefit, while the shortest PFS was observed in patients with del(17p) and/or del(11q).[26,27] Durable remission in M-IGHV disease with FCR after a median follow-up of 19 years from a Phase II study raised the possibility of a functional cure with FCR in this subgroup, especially in those achieving measurable residual disease (MRD) negativity at end-of-treatment.[28]

With the enthusiasm of a potential 'functional cure', it is important to consider treatment-related toxicity, in particular tMN, which was observed in a noteworthy 6.3% of patients in the previously mentioned data.[28] It is recognized that pre-existing clonal hematopoiesis of indeterminate potential (CHIP) may be a risk factor for tMN.[29] Therefore, rather than leaving behind a potential cure, perhaps aiming to optimize patient selection by administering FCR only to those with M-IGHV in the absence of *TP53* aberrations and no pre-existing CHIP may be a future research question.

Venetoclax-obinutuzumab

The efficacy of fixed-duration VO was established in the CLL13 and CLL14 trials for fit patients and patients with comorbidities, respectively.[30-33] In the CLL14 study, factors associated with shorter PFS included bulky disease (>5 cm), unmutated-IGHV (U-IGHV), and *TP53* aberrations. However, for the majority of patients, VO is an appealing option with a fixed treatment duration of 48 weeks and an expected significant treatment-free interval. After 6 years of follow-up in CLL14, time to next treatment was approximately 7 years (85 months) in patients with U-IGHV, and not reached in patients with M-IGHV. After 6 years of follow-up in CLL13, 83% of patients with U-IGHV and 96% of patients with M-IGHV have not started any new treatment.

The safety profile of VO appears favourable both in the short- and long-term, with the majority of adverse events (AEs) occurring during treatment (62.7%) and infrequent after treatment (9.9%).[30,32] A major concern with venetoclax is tumour lysis syndrome (TLS), which requires a 5-week dose ramp-up phase with close outpatient monitoring and, in rare cases, inpatient admission, which can be cumbersome. Despite this concern, the incidence of TLS is overall low at 1.4% described on trial and 5.1% in the real-world setting, all of which were solely biochemical.[33,34] Studies that prospectively explore alternative ramp-up schedules that may be more convenient for patients are awaited (e.g., NCT04843904, NCT06428019). While hematological AEs are common, other AEs of interest include infusion-related reactions (grade 3/4: 9%) and infections (grade 3/4: 17.5%).

In the era of COVID-19, the risk of B-cell depletion with CD20-targeted monoclonal antibodies needs consideration, since the risk of breakthrough infections, hospitalization, and death is noted to be higher in patients with hematologic malignancies compared to matched non-cancer controls, and lowest vaccine seropositivity is noted in patients with CLL and in those who had received an CD20-targeted monoclonal antibody within 12 months.[35-37] Despite the above, a Canadian study showed that in patients who received at least two doses of COVID-19 vaccination, the real-world mortality risk was low at <1%, even in patients who received anti-CD20 antibodies within the last year.[36,37] From that perspective, the most important measures to take are to ensure patients are vaccinated against COVID-19 prior to initiating therapy, keep testing kits at home, and are aware of their eligibility for COVID-19 therapeutics.

Oral Doublets: The Convenience of Two Oral Drugs Against the Risk of Cardiac Toxicity

Three cycles of ibrutinib monotherapy lead-in followed by a combination with venetoclax (IV) for 12 cycles has been investigated in the GLOW (patients >65 years or those with comorbidities) and CAPTIVATE (patients <70 years) trials,[38,39] leading to Health Canada approval for this combination in patients with CLL. The FLAIR trial in young, fit patients found that MRD-guided or maximum treatment duration of 6 years of IV was superior to FCR; however, this approach is unlikely to become standard practice in Canada, given that MRD testing is not widely available.[40] Notably, there are currently no published trials demonstrating the superiority of an MRD-guided approach to a fixed-duration approach.

The predominant safety concern observed in all trials was cardiac toxicity. In the CAPTIVATE trial, one sudden cardiac death (SCD, 1%) was observed in a male patient aged 54 years with a history of hypertension, dyslipidemia, and smoking. In the GLOW trial, four patients (4%) experienced SCD, all of whom had a high Cumulative Illness Rating Scale (CIRS) score and/or Eastern Cooperative Oncology Group (ECOG) performance status of 2, raising caution about the use of this regimen in patients with comorbidities. Rates of hypertension and atrial fibrillation/arrhythmia with IV appear to occur at similar frequencies as observed for ibrutinib monotherapy and remain a concern even with fixed-duration therapy.[38-40]

The recently published AMPLIFY trial studying fixed-duration acalabrutinib-venetoclax +/- obinutuzumab represents an alternative oral doublet with a more appealing safety profile.[41] However, this combination is not yet FDA- or Health Canada-approved.

Approach to High-risk Patients with *TP53* Mutations and/or del(17p)

It is well established that continuous BTKi treatment retains efficacy in patients with *TP53* aberrations. A pooled analysis of four trials of ibrutinib-treated patients, subgroup data from the ELEVATE-TN trial (acalabrutinib), and Arm C from the SEQUOIA trial (zanubrutinib) all demonstrated excellent PFS with the use of these agents, with 4-year PFS ranging from 76–79%.[42-44]

When considering fixed-duration options for this high-risk subgroup, the median PFS was 51.9 months in the CLL14 trial with VO (n=25).[33] Therefore, while BTKis remain the preferred treatment option for patients with high-risk disease, it is not unreasonable to consider fixed-duration VO for patients who highly value a treatment-free interval. Additionally, the CAPTIVATE trial, which included younger patients, demonstrated a 5.5-year PFS of 36% (95% CI: 17–55) with IV in this subgroup (n=27).[45]

Overall, the current favoured treatment option for high-risk patients is BTKi; however, patient preferences are important to consider, as the cumulative efficacy of fixed-duration approaches, including retreatment, has not yet been established. The efficacy of VO retreatment is under study (NCT04895436, NCT04523428). We look forward to the ongoing CLL17 trial, which will provide direct comparative data on fixed-duration IV and VO versus continuous ibrutinib therapy, although it will only include a subgroup of high-risk patients. The CLL16 trial enrolls only high-risk patients and will provide data to determine whether a fixed-duration triplet (acalabrutinib + VO) performs favourably to VO.

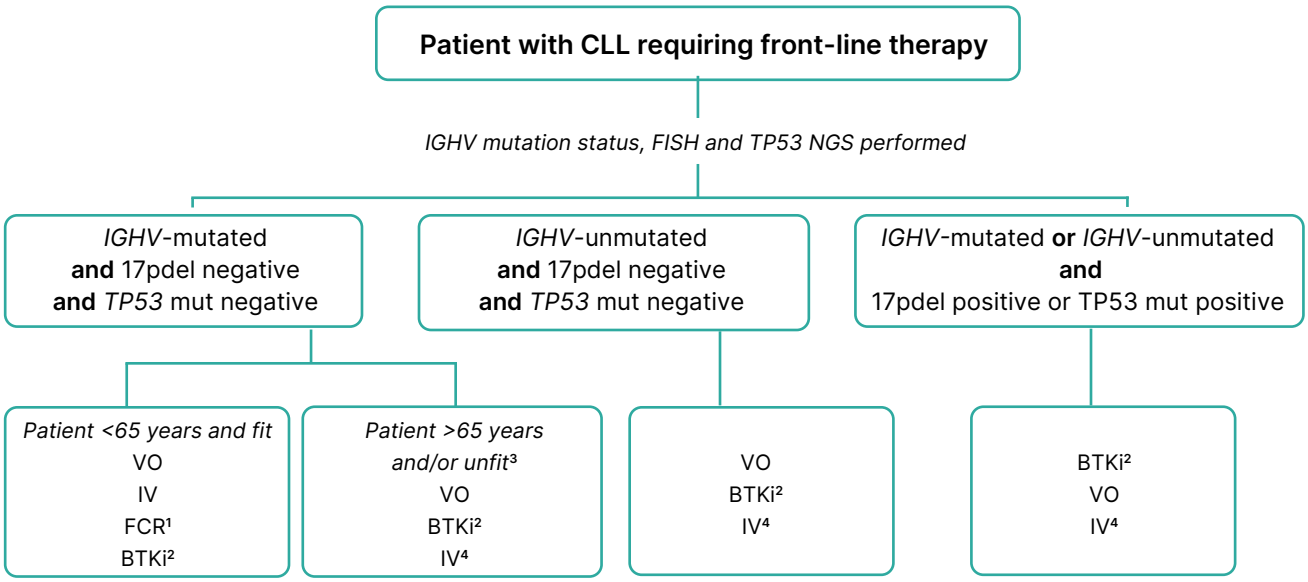


Figure 2. Treatment approach for CLL in the Canadian landscape; *courtesy of Chathuri Abeyakoon, MD and Abi Vijenthira, MD.*

[1]Additional considerations using currently available testing: absence of mutated IGHV subset 2, absence of 11qdel
[2]Second-generation BTKi (acalabrutinib, zanubrutinib) are preferred over ibrutinib
[3]In frail older patients with mutated IGHV in whom simpler time-limited therapy is preferred, chlorambucil-obinutuzumab (5-year PFS: 50%) is reasonable
[4]Caution in less fit patients due to risks of treatment-related mortality based on GLOW trial

Abbreviations: BTKi: Bruton's tyrosine kinase inhibitor; **CLL:** chronic lymphocytic leukemia; **FISH:** fluorescence *in situ* hybridization; **FCR:** fludarabine, cyclophosphamide, rituximab; **IGHV:** immunoglobulin heavy chain variable region; **IV:** ibrutinib, venetoclax; **mut:** mutation; **NGS:** next-generation sequencing; **PFS:** progression-free survival; **VO:** venetoclax, obinutuzumab; **yrs:** years

Conclusions

The decision between continuous versus fixed-duration treatment in front-line CLL is a personalized choice based on a thorough assessment and discussion with the patient regarding the risks versus benefits of each approach. Treatment choice should be dictated by CLL prognostic factors, comorbidities, and patient preferences. For the majority of patients, a fixed-duration treatment approach is favoured, which can balance efficacy, safety, and costs. Our approach outlined in **Figure 2** ranks treatment choices in order of preference. We also recommend reviewing national guidelines when considering state-of-the-art treatment approaches for patients with CLL in Canada.[46]

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Financial Disclosures

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Intensive Versus Non-intensive Therapy for Patients with Newly Diagnosed Acute Myeloid Leukemia (AML)

Karen W.L. Yee, MSc, MD, FRCPC

Introduction

Newly approved treatments have increased the options available for patients with acute myeloid leukemia (AML), but have also generated questions concerning the selection of the most appropriate therapy for a given individual (**Tables 1 & 2**).[1-13] The trials leading to the approval of these therapies were based on limited genetic data (e.g., cytogenetics, *FMS-like tyrosine kinase-3 [FLT3]* status) and clinical parameters (e.g., age, comorbidities, therapy, or secondary AML). Data concerning effectiveness or lack of efficacy of a drug or drug regimen in specific AML subgroups is often determined after drug approval. For example, venetoclax (VEN) + azacitidine (AZA) lower intensity therapy (LIT), which is approved for the treatment of patients with newly diagnosed AML deemed ineligible for intensive chemotherapy (IC) or aged >75 years, was found to have limited efficacy in patients with mutated *TP53*.[14,15] Despite the regulatory approved indications for VEN-based LIT, some older and younger patients can be selected for either LIT or IC. Furthermore, with the availability of maintenance therapy after IC16,

several important questions have emerged regarding the role of IC in older patients.

No published prospective studies have compared IC with LIT in "fit" patients with newly diagnosed AML to inform treatment choice. Two retrospective propensity score matched real-world data analyses of outcomes in patients with newly diagnosed AML (irrespective of the genetic profile) who received induction with VEN + AZA or IC, indicated no difference in overall survival (OS).[17,18] However, one study showed improved complete remission (CR) and/or allogeneic hematopoietic stem cell transplant (alloHCT) rates in favour of IC (60.9% vs. 44.2%, *P* = 0.006 and 18.1% vs. 8.0%, *P* = 0.012, respectively).[17] Other single-centre retrospective studies comparing VEN + AZA with IC have yielded conflicting results.[19,20] None of these studies provided information concerning the use of oral AZA maintenance therapy. The studies did suggest that outcomes may be dependent on specific genetic abnormalities and/or clinical factors.[17,19,20] Currently, several Phase 2 trials are comparing VEN + AZA with IC in adult patients with newly diagnosed AML (NCT04801797, NCT05904106, NCT05554406, NCT05554393).

Here, two case scenarios will be discussed to highlight issues surrounding treatment choice: **a)** fit individuals who are ≥75 years with newly diagnosed European LeukemiaNet (ELN)-defined favourable-risk AML and **b)** IC eligible persons who are ≥18 years with newly diagnosed ELN-defined poor-risk AML, who require alloHCT in first complete remission (CR1) with curative intent.

Case 1

A 75-year-old woman with a history of type 2 diabetes mellitus, hypertension, and dyslipidemia presented with a white blood cell count (WBC) of 66.7 × 10^9/L, 2.27 × 10^9/L neutrophils, and 103 × 10^9/L platelets, with 27% circulating blasts. The diagnostic workup showed 84% marrow myeloblasts expressing CD33, CD45, CD117, CD123, and myeloperoxidase (MPO). Cytogenetics revealed a normal karyotype in all 20 metaphases. Rapid molecular testing identified an *NPM1* mutation and the absence of *FLT3* internal tandem duplication (ITD) or tyrosine kinase domain (TKD) mutations. Results from a next-generation sequencing (NGS)-based gene panel would not be available for another 2 weeks. This was consistent with a presumptive diagnosis of AML with mutated *NPM1*,[21,22] pending additional genetic results. Her Eastern Cooperative Oncology Group (ECOG) performance status was 1. The patient received cytoreductive hydroxyurea and allopurinol. Should she receive IC or LIT with VEN + AZA?

What are the Outcomes with IC Followed by Oral AZA Maintenance Treatment Compared with VEN + AZA in Older Patients with *NPM1*-mutated AML?

Approximately 30% of AML cases harbor *NPM1* mutations.[23] In both the ELN 2022 genetic risk classification, which was developed predominantly from younger patients receiving IC, and the newer ELN 2024 genetic risk classification for LIT, the presence of an *NPM1* mutation is considered favourable in the absence of adverse cytogenetics and *FLT3*-ITD mutation or absence of signalling mutations.[24,25] However, *NPM1*-mutated AML remains a very heterogenous disease with outcomes dependent not only on the presence of co-occurring genetic abnormalities (e.g., *FLT3*-ITD, *DNMT3A*, *WT1*), but also on clinical parameters (e.g., age and WBC at presentation), type of *NPM1* mutation, and measurable residual disease (MRD) status.[23,26]

Two retrospective studies compared IC with VEN + a hypomethylating agent (HMA) in older patients with *NPM1*-mutated AML.[27,28] In multivariate analysis, no statistically significant difference in OS was found between the two groups; however, information on the use of oral AZA maintenance therapy, subsequent lines of therapy, and MRD status were not available. One-study suggested that patients with *NPM1*-mutated AML with normal cytogenetics and without *FLT3*-ITD mutation may benefit from IC over VEN + HMA.[28]

IC Followed by Oral AZA Maintenance

Swedish registry data showed that 66.4%, 44.5%, and 22.9% of patients aged 70–74 years, 75–79 years, and 80–84 years, respectively, can be considered fit for IC.[29] Early deaths in older individuals (i.e., ≥60 years) treated with IC varied from 6% to 12% in randomized trials(**Table 1**),[1,2,30] whereas retrospective data from European registries have documented a 30-day mortality of 13%.[31]

A median OS of ~42 months or a 2-year OS of ~56% can be achieved in older patients with *NPM1*-mutated AML who received IC.[32-34] Up to 80% of patients with *NPM1*-mutated AML can achieve NPM1 MRD negativity after 2 cycles of IC, which is associated with improved

OS with a lower risk of relapse.[26] Induction chemotherapy is typically followed by 2 to 4 cycles of consolidation therapy depending on the treatment regimen.[16,24,35,36] Oral AZA maintenance therapy for older patients with AML with intermediate-or poor-risk cytogenetics in CR1 after IC has been shown to improve survival (from the time of randomization) compared to placebo (i.e., 24.7 months vs. 14.9 months, respectively; *P* <0.001) with estimated 3-year and 5-year OS rates of 37.4% and 26.5% compared to 27.9% and 20.1%, respectively.[16,36] Treatment with oral AZA also resulted in a higher conversion from MRD positive status (as measured by multiparameter flow cytometry [MFC]) at baseline to MRD negative status during treatment compared with placebo (37% vs. 19%; odds ratio: 2.50 [95% confidence interval [CI]: 1.35–4.61]).[37] Retrospective analysis involving 99.4% of participants who had mutational data available at the time of AML diagnosis revealed that patients with *NPM1*-mutated AML in CR1 with or without MRD negativity by MFC who received oral AZA maintenance had a median OS of 48.6 months and 46.1 months, respectively (compared with 31.4 months and 10 months, respectively, in the placebo arm).[38]

Is There Any Benefit for Administering Gemtuzumab Ozogamicin (GO) with IC in Patients with NPM1-mutated AML?

GO is approved in combination with daunorubicin and cytarabine (3+7) in the treatment of patients with newly diagnosed CD33-positive AML with favourable or intermediate-risk cytogenetics (**Table 1**). Administration of GO with IC in patients with newly diagnosed *NPM1*-mutated AML is associated with increased MRD negativity and decreased risk of relapse; however, this has not been shown to lead to improved event-free survival (EFS) or OS, potentially due to increased early death rates in participants >70 years of age who received GO.[33,39,40]

LIT with VEN + AZA

Lower intensity VEN-based regimens (i.e. VEN + AZA or VEN + LDAC) are associated with early death rates of 7–13% (**Table 2**).[9-12] Treatment with VEN + AZA in IC-ineligible patients with newly diagnosed AML yielded a median OS of 14.7 months with an estimated 2-year OS of 37.5%.[9,10] However, patients with *NPM1*-mutated AML without signalling mutations (i.e., absence of *FLT3-ITD, KRAS, NRAS*, and *TP53* mutations) had a median OS of 39 months.[41]

Up to 42% of patients can achieve MRD negativity by MFC during the course of treatment with VEN + AZA; however, only 21% achieved MRD negativity after 4 cycles of therapy in this study.[42] Achievement of *NPM1* MRD negativity after 4–6 cycles of VEN-based LIT has been associated with improved OS.[26,43] Although achievement of an MRD negative CR after IC is associated with improved OS and relapse-free survival (RFS), the role of MRD in patients receiving LIT requires further evaluation.[42,44,45] Treatment with VEN-based LIT is long-term and continues until signs of disease progression, unacceptable toxicity, or patient request.[9,11] Most patients require VEN dose modifications to manage cytopenias without adversely affecting survival.[46] Among the 68% VEN + AZA-treated patients who achieved a CR or CR with incomplete count recovery (CRi), the median number of treatment cycles was 13 (range: 1–46), with 76% of patients receiving ≥6 cycles. The number of cycles that patients with *NPM1*-mutated AML received was not specified. A small number of patients in CR have discontinued VEN-based LIT with a median treatment-free survival of 16 to 46 months.[26,47,48]

Is the Quality of Life (QoL) Impacted in Patients Receiving IC Followed by Oral AZA Maintenance or with VEN + AZA?

IC is administered for a limited treatment period and is associated with short-term toxicities.[49,50] QoL improves during treatment (i.e., from induction to consolidation chemotherapy), independent of age.[49,50] Oral AZA maintenance chemotherapy is easy to administer, convenient for both patients and caregivers, results in fewer clinic or hospital visits, and abrogates injection site reactions without decreasing favourable health-related QoL for patients with AML in CR (compared to placebo).[16,51]

In contrast, treatment with VEN + AZA is prolonged, increases caregiver burden, and requires multidisciplinary care, serial visits to the hospital or clinic for AZA injections, and several VEN dose and/or cycle adjustments to allow for count recovery.[10] QoL assessments were similar between VEN + AZA vs. placebo + AZA (*P* = 0.65,) and there was a trend of longer time to deterioration in global health score in the VEN + AZA arm compared to placebo + AZA.[10] Obviously, no QoL assessments comparing VEN + AZA to placebo alone has been performed.

	CPX-351[¶], [1,2,20,71] (*N = 153*)	GO[§] + 3+7[3,4] (*N = 139*)	Midostaurin[¥] + 3+7[6,7] (*N = 360*)	Quizartinib[‡] + 3+7[8] (*N = 268*)
Characteristics				
Median age, y (range) Age >75 y	67.8[a] Not provided but no patients >75 y	62.8 (59.3–66.8)b 0[c]	48.6 (18–60.9)d 0[c]	56 (23–75)[e] Not provided but no patients >75 y
***De novo* AML**	41 (26.8%)	139 (100%)	---	243 (91%)
Therapy-related AML (tAML)	30 (19.6%)	0[c]	0[c]	0[c]
Secondary AML (sAML)	82 (53.6%)	0[c]	---	25 (9%)
Cytogenetic risk group Good Intermediate Poor	 7 (4.9%) 64 (44.8%) 72 (50.3%)	 3 (2%) 91 (65%) 28 (20%)[d]	 16/269 (5.9%) 231/269 (85.9%) 22/269 (8.2%)	 14 (5%) 197 (74%) 19 (7%)
Gene mutations *FLT3-ITD/TKD* *TP53*	 22/138 (15.9%) 24 (15.6%)	 *FLT3-ITD* 22/137 (16%) ---	 *FLT3-ITD* 279 (77.5%) / *FLT3-TKD* 81 (22.5%) ---	 *FLT3-ITD* 268 (100%) ---
Outcomes				
CR + CRi All tAML sAML Poor-risk cytogenetics FLT3-ITD/TKD *TP53*	 73 (47.7%; CR 37.3%) 14/30 (46.7%; CR 36.7%) 36/82 (43.9%: CR 32.9%) 31/72 (43.1%; CR 34.7%) 15/22 (68.2%; CR 54.5%) 7/24 (CR 29.1%)	 CR + CRp 113 (81%; CR 73%) ---[c] ---[c] 14/28 (50%; CR not provided) FLT3-ITD 21/22 (95.5%; CR not provided) Not done	 CR 212/360 (59%); expanded CR 244/360 (68%) ---[c] --- --- CR 212/360 (59%); expanded CR 244/360 (68%) ---	 192 (72%; CR 54.9%) ---[c] --- --- FLT3-ITD 192 (72%; CR 54.9%) ---

	CPX-351¶, [1,2,20,71] (*N = 153*)	GO§ + 3+7[3,4] (*N = 139*)	Midostaurin¥ + 3+7[6,7] (*N = 360*)	Quizartinib‡ + 3+7[8] (*N = 268*)
Median duration of response, mos (95% CI)	6.93	---	---	38.6 (21.9-not estimable)
Median follow-up, mos	60.9	47.6	59	39.2
Median OS, mos (95% CI)	9.33 (6.37–11.86)	27.5 (21.4–45.6)	74.7 (31.5-not reached)	31.9 (21-not estimable)
Poor-risk	6.42 (4.96–9.66)	---	---	Not reached
cytogenetics	10.25 (5.62–14.95)	---	---	FLT3-ITD 31.9 (21-not estimable)
FLT3-ITD/TKD	4.5 (2.9–7.6)	---	---	---
TP53				
OS, % (95% CI)	18 (12-25) at 5y	---	43.7 (38.7-49.3) at 10y	---
30-day mortality	5.9%	3.8%	---	6%

Table 1. Front-line Phase 3 Randomized Clinical Trials with Intensive Chemotherapy (IC); *modified from Tang et al.*

¶ Approved for the treatment of adults with newly diagnosed therapy-related AML (t-AML) or AML with myelodysplasia-related changes (AML-MRC).
§ Approved for the treatment of newly-diagnosed CD33-positive AML in adults in combination with daunorubicin and cytarabine for adults with newly-diagnosed AML, except acute promyelocytic leukemia (APL).
¥ Approved for use with standard cytarabine and daunorubicin induction and cytarabine consolidation for the treatment of adults with newly diagnosed *FLT3*-mutated AML.
‡ Under Health Canada review for regulatory approval for use with standard cytarabine and anthracycline induction and cytarabine consolidation, and as maintenance monotherapy following consolidation chemotherapy, for the treatment of adult patients with newly diagnosed AML that is *FLT3*-ITD-positive.

[a] Eligible age for enrolment onto study: 60–75 y.
[b] Eligible age for enrolment onto study: 50–70 y.
[c] This group of patients were not eligible for the study.
[d] Cytogenetics not available in 17 patients (12%); [d] eligible age for enrolment onto study: 18–<60 y.
[e] Eligible age for enrolment onto study: 18–75 y.

Abbreviations: 3+7: daunorubicin (or idarubicin) + cytarabine; **AML:** acute myeloid leukemia; **CI:** confidence interval; **CR:** complete remission; **CRp:** CR with incomplete platelet recovery; **CRi:** complete remission with incomplete count recovery; **GO:** gemtuzumab ozogamicin; **mos:** months; **OS:** overall survival; **y:** years

	VEN + AZA[¶] [9,10] (*N = 286*)	VEN + LDAC[§] [11,12] (*N = 143*)	AZA + ivosidenib[¥] [13] (*N = 72*)
Characteristics			
Median age, y (range)	76 (59–91)	76 (36–93)	76 (58–84)
Age >75 y	174 (61%)	82 (57%)	39 (54%)
***De novo* AML**	214 (75%)	85 (59%)	54 (75)
Therapy-related AML (tAML)	26 (9%)	6/58 (10%)	2 (3%)
Secondary AML (sAML)	46 (16%)	52/58 (90%)	16 (22%)
Prior HMA	0[a]	28 (20%)	0[a]
Cytogenetic risk group			
Good	0[a]	1 (1%)	3 (4%)
Intermediate	182 (64%)	90 (63%)	48 (67%)
Poor	104 (36%)	47 (33%)	16 (22%)
Gene mutations			
FLT3-ITD/TKD	29/206 (14%)	20/112 (18%)	4/58 (7%)
IDH1/2	61/245 (25%)	21/112 (19%)	*IDH1 72* (100%)
TP53	38/163 (23%)	22/112 (20%)	5/58 (9%)
Outcomes			
CR + CRi			
All	191 (66.8%; CR 36.7%)	69 (48%; CR 27%)	39 (54%; CR 47%)[c]
tAML	s/tAML 48/72 (66.7%)	s/tAML 21/58 (36%; CR 16%)	---
sAML			---
Poor-risk cytogenetics	55/104 (52.9%)	13/47 (28%; CR 17%)	---
Prior HMA	---[a]	7/28 (25%; CR 7%)	---[a]
FLT3-ITD/TKD	21/29 (72.4%)	9/20 (45%; CR25%)	---
IDH1/2	47/63 (74.6%)[b]	12/21 (57%; CR 38%)	39 (54%; CR 47%) for *IDH1*
TP53	21/38 (55.3%)	4/22 (18%; CR 5%)	---

	VEN + AZA[¶] [9,10] (*N = 286*)	VEN + LDAC[§] [11,12] (*N = 143*)	AZA + ivosidenib[¥] [13] (*N = 72*)
Time to response, mos (range)	1.3 (0.6–9.9) for CR + CRi	Before initiation cycle 2: 34% for CR + CRi	2.1 (1.7–7.5)
Median duration of response, mos (95% CI)	18.2 (13.6–23.1) for CR + CRi	11.7 for CR + CRi	22.1 (13-not estimable)
Median follow-up, mos	43.2	17.5	12.4
Median OS, mos (95% CI)	14.7 (12.1–18.7)		
Poor-risk cytogenetics	---	8.4 (5.9–10.1)	24 (11.3–34.1)
Prior HMA	---[a]	4.4 (3–6.4)	---
IDH1/2	19.9 (12.2-27.7)/IDH1 10.2 (2.3-25.1)	5.6 (3.4–9.6) ---	---[a] IDH1 24 (11.3–34.1)
OS, % (95% CI)	37.5 (31.8-43.3) at 2 y	---	---
30-day mortality	21/286 (7%)	18/143 (13%)	---

Table 2. Front-line Phase 3 Randomized Clinical Trials with Lower Intensity Therapy (LIT) for Patients Ineligible for Intensive Chemotherapy (IC) or age >75 y; *modified from Tang et al.*

[¶] approved for the administration of venetoclax in combination with AZA for the treatment of newly-diagnosed AML in adults who are >75 years, or who have comorbidities that preclude use of intensive induction chemotherapy.
[§] approved for the administration of venetoclax in combination with LDAC for the treatment of newly-diagnosed AML in adults who are >75 years, or who have comorbidities that preclude use of intensive induction chemotherapy.
[¥] approved for the administration of ivosidenib in combination with AZA for the treatment of adult patients with newly diagnosed AML with an *IDH1* R132 mutation who are not eligible for intensive induction chemotherapy

[a] this group of patients were not eligible for the study.
[b] CR + CRi for *IDH1* mutated 13/23 (56.5%) and for *IDH2* mutated 34/40 (85%).
[c] response by 24 weeks

Abbrviations: AZA: azacitidine; **CI:** confidence interval; **CR:** complete remission; **CRh:** CR with hematologic improvement; **CRi:** complete remission with incomplete count recovery; **HMA:** hypomethylating agent; **LDAC:** low-dose cytarabine; **MDS:** myelodysplastic syndrome; **mos**: months; **NR:** not reached; **ORR:** overall response rate (CR + CRi + morphologic leukemic-free state [MLFS]); **OS:** overall survival; **y:** year

Case 1 Patient Update

The patient from case 1 received IC with 3+7 (i.e., daunorubicin 60 mg/m^2/d and cytarabine 100 mg/m2d),[35,53] without the addition of GO. Her course in hospital was complicated by proctocolitis, bacteremia in the setting of line-associated thrombosis in the left basilic vein, and the development of platelet alloantibodies. She achieved a CR with MRD negativity by both MFC and molecular analysis, with undetectable *NPM1* transcripts after 1 cycle of induction chemotherapy. During this interval, NGS at diagnosis was reported and revealed the presence of pathogenic Type A *NPM1* c.860_863dupTCTG p.(Trp288fs) and TET2 c.4082delG p.(Gly1361fs) variants. Hence, the only adverse features associated with *NPM1*-mutated AML were her increased age and elevated WBC at presentation. She completed outpatient consolidation therapies with an end-of-treatment bone marrow (BM) showing an ongoing morphological remission with both MFC and *NPM1* MRD negativity. The patient started maintenance therapy with oral AZA with serial BM assessments to monitor the MRD status.

What is the Role of Serial MRD Assessment?

Despite achieving *NPM1* MRD negativity after IC, patients remain at a relapse risk of 22% to 40% at 3 years.[26,53] The benefit of oral AZA maintenance was observed irrespective of MRD status at baseline, with improved OS in those who were MRD negative.[36,37] The patient had serial BM analyses performed every 3 months for *NPM1* MRD assessments,[54] as documentation of a molecular relapse will lead to hematological relapse without therapeutic intervention.[53,55] She has been receiving oral AZA maintenance therapy for 17 months with ongoing *NPM1* MRD negativity.

What is the Duration of Maintenance Therapy with Oral AZA?

There is a lack of data, including the use of MRD, to help guide decisions concerning when to discontinue oral AZA maintenance therapy. In the Quazar AML-001 trial, oral AZA maintenance was administered until patients were no longer deriving benefit.[16,36] At 55.5 months of follow-up, only 11% of patients were still receiving oral AZA maintenance. Overall, 23% of patients had received ≥36 treatment cycles (~3 years) and 14% received ≥60 cycles.

Case 2

A 58-year-old man with a prior history of treated diffuse large B-cell lymphoma presented to the local emergency department with a temperature of 38.6°C, coughing, and rhinorrhea. A CT scan of the chest demonstrated left lower lobe pneumonia. Blood cultures were negative for bacterial growth. Bloodwork revealed WBC: 0.8 × 10^9/L, neutrophils: 0.2 × 10^9/L, platelets: 47 × 10^9/L, with rare circulating blasts. BM aspirate and biopsy showed ~22% blasts expressing CD13, CD33, CD34, CD117, and HLA-DR. Cytogenetics revealed 44,XY,der(1)r(1;?)(p36.?3q32;?),add(5)(p15),add(5)(q13),add(9)(q34),-17,-18[8]/46,XY[2]. Rapid molecular testing did not detect any *NPM1* or *FLT3* mutations. Results from the NGS-based gene panel would not be available for another 2 weeks. These findings were consistent with a presumptive diagnosis of AML, myelodysplasia-related post-cytotoxic therapy,[21,22] pending additional genetic results. The patient received antimicrobials to treat pneumonia. He had no other comorbidities and his ECOG performance status was 1.

What is This Patient's Prognosis?

The patient has therapy-related AML with a complex, monosomal karyotype involving monosomy 17. Twenty to forty percent of patients with therapy-related AML, 70% of patients with complex karyotype, and up to 67% with monosomy 17 and/or del(17p), will have a TP53 mutation.[14,15,56,57] Therefore, he had a high likelihood of having a *TP53* mutation.[22]

Patients with AML and a complex karyotype with or without a *TP53* mutation are considered adverse risk by ELN 2022 with a median OS of 7–10 months.[24,58,59] According to the ELN 2024 genetic risk classification for LIT, a complex karyotype is considered favourable or intermediate risk depending on the absence or presence of signalling mutations, with a median OS of ≥24 months and 12–13 months, respectively.[25,41] *TP53* mutations are considered an adverse risk with a median OS of 5–8 months.[25,41] Real-world evidence confirms the poor outcomes of patients with TP53-mutated AML with a median OS of 7.3 months, irrespective of the type of treatment administered (i.e., IC, VEN-based LIT, or single agent HMAs).[60] The only potential curative treatment for patients with *TP53*-mutated AML is an alloHCT in CR1.[61-66] However, only up to 16% of patients can receive an alloHCT.[61-64]

Multivariate analysis demonstrated improved OS in patients who were transplanted in CR1 and who had chronic graft-versus-host disease (GVHD), single-hit TP53 mutations, and non-complex karyotypes.[62-64] It remains unclear whether the intensity of the treatment (i.e., IC vs. LIT) used to achieve a CR prior to alloHCT affects outcomes in patients with *TP53*-mutated AML.[64,67-69] It is also unknown whether pre-transplant MRD positivity predicts for worse OS and increased relapse risk in this group of patients.[67]

Should the Patient Receive IC or LIT with VEN + AZA to Achieve a CR Followed by alloHCT?

IC in this clinical situation yields CR rates of 28% to 42%.[57] CPX-351 (daunorubicin and cytarabine liposome for injection) is approved for the treatment of adults with newly diagnosed therapy-related AML or AML with myelodysplasia-related changes (**Table 1**). Treatment of patients with AML with poor-risk cytogenetics with CPX-351 is associated with composite CR (i.e., CRc; CR + CRi) rates of 43.1% (CR: 34.7%).[1,2,70,71] In patients with *TP53*-mutated AML, CPX-351 yields a CRc rate of 29% with a median remission duration of 8.1 months and a median OS of 4.5 months.[1,2,70,71] Patients with ELN 2022 adverse risk AML are less likely to achieve MRD negativity than those with favourable or intermediate risk AML.[72]

Treatment with VEN + AZA yields CRc rates of 70%, a median remission duration of 18.4 months, and a median OS of 23.4 months in patients with AML with poor-risk cytogenetics without *TP53* mutations.[73] In contrast, the CRc rate was only 41%, the median remission duration 6.5 months, and the median OS 5.2 months in patients with poor risk cytogenetics and mutated *TP53*.[73] Utilization of VEN + HMA, rather than IC, may decrease treatment-related toxicities and delayed referrals to alloHCT, while increasing the proportion of patients who receive an alloHCT.[67]

Case 2 Patient Update

The patient received VEN + AZA therapy and achieved a morphological CR after 1 cycle of therapy. The BM sample sent for MFC MRD assessment was inadequate. During this period, NGS from the diagnostic BM revealed a Tier I *TP53* c.659A>G p.(Tyr220Cys) VAF 22%. Repeat BM assessment after cycle 2 of VEN + AZA revealed ongoing CR with MRD positivity by MFC at 0.17%. The patient received another 2 cycles of VEN + AZA prior to proceeding to alloHCT with a matched unrelated donor. Pre-transplant BM showed ongoing CR with routine flow analysis showing <1% CD34-positive myeloblasts. He is currently 4 months post-alloHCT, without signs of GVHD.

Conclusion

Treatment of patients with newly diagnosed AML is becoming more nuanced with the choice of therapeutic regimen dependent on patient-related factors (including age, presence of comorbidities, and fragility) and disease biology, such as cytogenetic abnormalities, gene mutations, and co-mutations, and the persistence of leukemic cells after therapy (i.e., MRD). This also highlights the need for rapid turnaround times for genetic test results to provide upfront risk stratification, guiding treatment decision-making and subsequent disease monitoring. The ongoing randomized Phase 2 studies comparing IC with VEN + AZA are expected to provide further information concerning the appropriate treatment for newly diagnosed adult patients with AML.

Off-Label Drug Use
This paper discusses the use of venetoclax and azacitidine in intensive chemotherapy-eligible patients with newly diagnosed AML.

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Management of Newly Diagnosed Primary Central Nervous System Lymphoma

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Introduction

The last decade has witnessed significant progress in the clinical management of patients with newly diagnosed primary central nervous system (CNS) diffuse large B-cell lymphoma (PCNS-DLBCL, hereafter referred to as PCNSL). Data from several clinical trials have demonstrated the potential for long-term remission in a proportion of patients, particularly those eligible for intensive multi-agent chemotherapy approaches.[1-3] High-dose methotrexate (HD-MTX)-based induction regimens remain standard-of-care globally for both younger and older patients with newly diagnosed PCNSL. However, with clinical trial data demonstrating the efficacy of multiple regimens (differing in partner chemotherapy agents, hematological toxicity, and MTX dose density), but with few randomized comparisons, the optimal induction regimen remains unclear.

Consolidation therapy is key to survival outcomes in PCNSL. Thiotepa-based autologous stem cell transplantation (TT-ASCT) has been widely adopted as the consolidation therapy of choice for patients ≤70 years. However, it is increasingly recognized that appropriately selected patients older than 70 years can also benefit from TT-ASCT consolidation.[4,5] In parallel, declining rates of whole-brain radiotherapy (WBRT) have been observed due to significant risk of neurotoxicity, particularly in patients aged ≥60 years.

This review summarises the contemporary clinical management of patients with newly diagnosed PCNSL. We focus on key diagnostic considerations, the landscape of evidence-based first-line treatments, and practical guidance for treatment selection and delivery. We also briefly discuss specific scenarios, including human immunodeficiency virus (HIV)-associated PCNSL and vitreoretinal involvement in the context of PCNSL.

Diagnosis and Staging

PCNSL, defined as large B-cell lymphoma (LBCL) arising from the parenchyma of the brain or spinal cord or leptomeninges, represents up to 4% of all brain cancers.[6] Patients with a suspected diagnosis of PCNSL should undergo whole-brain magnetic resonance imaging (MRI) with contrast, which typically reveals solitary (65%) or multifocal (35%) gadolinium-enhancing parenchymal lesions. Exclusive leptomeningeal involvement is rare. An early imaging review by an expert in neuroradiology is recommended. All efforts should be made to avoid corticosteroid use prior to biopsy due to an increased risk of a non-diagnostic sample.[7] Surgical resection does not improve outcomes, and less-invasive image-guided stereotactic approaches are therefore recommended.[6] Confirmation of diagnosis should involve a specialist hematopathologist review of tumour tissue. Typical histopathologic findings are a non-germinal centre LBCL phenotype; CD10 and Epstein-Barr virus (EBV)-positivity are uncommon and should prompt consideration for systemic lymphoma and immunodeficiency-associated lymphoma, respectively.[8] A minority of cases are diagnosed based on cytology supported by flow cytometry of cerebrospinal fluid (CSF).[7]

All patients should undergo body computed tomography (CT) or positron emission tomography (PET)/CT to exclude systemic lymphoma. An MRI of the spine is indicated for patients with relevant clinical symptoms or signs. Bone marrow biopsy (BMB) is not routinely recommended

for patients with a normal pattern of systemic fluorodeoxyglucose (FDG)-uptake on PET/CT.[6] BMB may also be considered if the clinical context suggests the possibility of underlying indolent lymphoma (e.g., presence of a paraprotein, cytopenias, or CD10-positive disease). It is good practice to also perform testicular ultrasound given the uncertain sensitivity of PET/CT for excluding testicular disease.

Expert ophthalmologic examination is recommended in all cases to exclude vitreoretinal lymphoma (VRL), which is present in up to 15% of PCNSL and is often asymptomatic.[9] In the context of biopsy-confirmed PCNSL, vitreous sampling or vitrectomy is not required to confirm VRL.

Where possible, CSF samples should be analyzed for cell count, protein levels, cytology, and flow cytometry. CSF abnormalities portend a poorer prognosis, and if CSF involvement is confirmed on cytology/flow cytometry, repeat sampling is required for response assessment.

Treatment of Newly Diagnosed PCNSL

General Considerations

Rituximab and HD-MTX-based regimens are standard-of-care for remission induction and are deliverable in the majority of patients, including those ≥60 years.[1,10,11] HD-MTX-based regimens require specific supportive care to mitigate serious toxicities and are best delivered at centres with lymphoma expertise. HD-MTX should be given as a short infusion (over 2–4 hours) at a dose of ≥3g/m^2 to optimize delivery across the blood-brain barrier (BBB).

HD-MTX can generally be given at full doses if the creatinine clearance is ≥50mL/min; dose adjustments or alternative therapies should be considered if the creatinine clearance is lower or if there are other risk factors for MTX toxicity.[12]

Decision-making for treatment can be initially informed by a patient's potential fitness for TT-ASCT (**Figure 1**). This is a clinical judgement based on a composite of age, organ function, comorbidities, and Eastern Cooperative Oncology Group performance status (ECOG PS) (considering both premorbid and lymphoma-related PS). For patients whose fitness for TT-ASCT is uncertain at initial diagnosis, re-evaluation should be undertaken dynamically during the early remission induction phase. **Table 1** summarizes the results of key clinical trials informing current treatment approaches.[13]

Younger Patients Fit for Intensive Treatment

Intensive remission-induction therapy with the intention to proceed to full-dose TT-ASCT should be considered in fit patients up to the age of 70. In this population, clinical trials have demonstrated improved event-free survival, quality of life, and neurocognitive outcomes with TT-ASCT compared to WBRT consolidation,[1,2] and improved overall survival (OS) with TT-ASCT compared to consolidation with further conventional dose chemotherapy.[14]

Various induction regimens, centred around a rituximab and HD-MTX backbone, have been demonstrated to be efficacious in large prospective trials. Based on the randomized IELSG32 trial, the preferred approach in many countries is four cycles of MATRix (HD-MTX, high-dose cytarabine [HD-AraC], thiotepa, and rituximab), followed by BCNU/TT-ASCT consolidation.[1] Importantly, real-world data suggest the IELSG32 approach should only be considered for patients who would have been trial-eligible (age ≤65 years and ECOG PS ≤3 or 66–70 years and ECOG PS ≤2). In a real-world European and UK study, patients with age or ECOG PS outside of IELSG32 eligibility criteria experienced first-cycle intensive care unit (ICU) admission rates of 11%, compared to 5% for IELSG32-eligible patients; the overall MATRix-related treatment-related mortality (TRM) was 6%.[15] Institutional experience with the required supportive care and expected toxicity of MATRix, including dose reductions, likely results in improved outcomes. A 25% dose reduction of cytarabine (i.e., omission of one dose) should be considered if the preceding cycle was complicated by febrile neutropenia.[16]

TT-ASCT is generally considered for patients with non-progressive disease (complete remission [CR], partial remission [PR], or stable disease [SD]); while also feasible in the setting of progressive disease (PD), these patients have poorer survival outcomes.[2] A reasonable alternative approach for patients with PD is to use a non-cross-resistant chemotherapy regimen (e.g., RICE [rituximab, ifosfamide, carboplatin, etoposide] or TIER [thiotepa, ifosfamide, etoposide, rituximab])[16,17] or WBRT, in order to improve response status prior to ASCT. Full-dose thiotepa (20mg/kg) conditioning is generally recommended in younger, fit patients. Although retrospective data show that 10mg/kg thiotepa (TT10-ASCT) may achieve equivalent outcomes

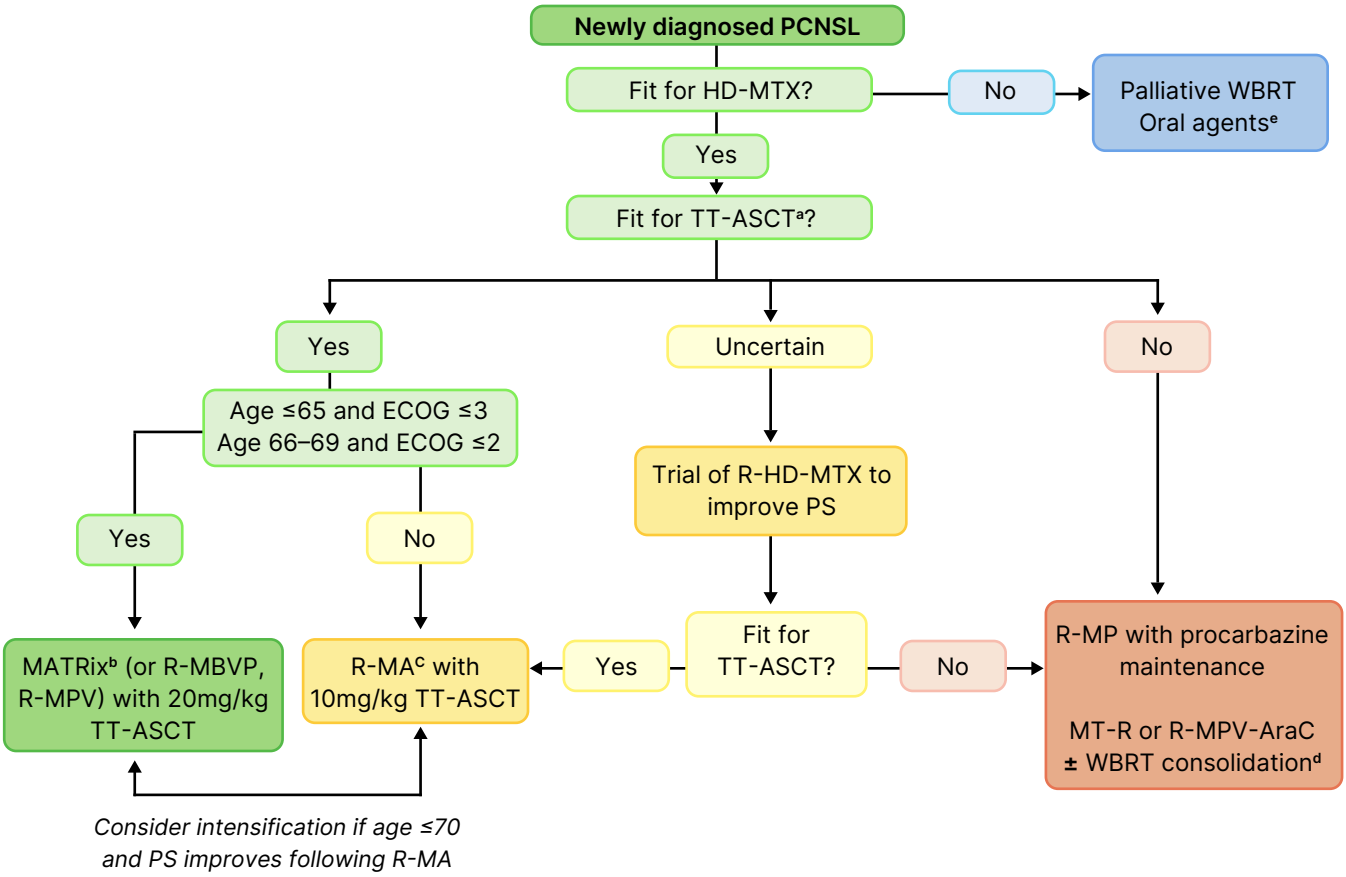


Figure 1. Suggested treatment algorithm for newly-diagnosed PCNSL; *courtesy of Diva Baggio, MD and Chris P. Fox, MBChB, FRCP, FRCPath, PhD.*

[a]Dynamic re-assessment of fitness for transplant should be performed at each clinical review.
[b]MATRix preferred due to randomised data.
[c]Consider empiric dose-reduction to two or three (rather than four) doses of cytarabine per cycle, and increasing total cycles to 3-4, particularly for patients with uncertain fitness for TT-ASCT.
[d]The PFS benefit of WBRT should be weighed against the risk of possible neurotoxicity and impact on quality of life.
[e]Options include palliative temozolomide, lenalidomide, or Bruton tyrosine kinase inhibitors.

Abbreviations: HD-MTX: high dose methotrexate; **TT-ASCT:** thiotepa autologous stem cell transplant; **WBRT:** whole brain radiotherapy; **MATRix:** methotrexate, cytarabine, thiotepa, rituximab; **R-MBVP:** rituximab, methotrexate, BCNU, etoposide, prednisolone; **R-MPV(-AraC):** rituximab, methotrexate, procarbazine, cytarabine; **R-MA:** rituximab, methotrexate, cytarabine; **R-MP:** rituximab, methotrexate, procarbazine; **MT-R:** methotrexate, temozolomide, rituximab

compared to 20mg/kg[18], a dose also supported by prospective studies in patients ≥65 years[4], prospective studies in younger patients are lacking. BEAM (BCNU, etoposide, cytarabine, melphalan) and other non-TT-containing regimens are not recommended due to lower efficacy in CNS lymphoma.[19]

Older Patients Fit for Intensive Treatment

Older fit patients eligible for TT10-ASCT may be considered for the MARTA treatment paradigm.[4] This single-arm, Phase II study of patients ≥65 years demonstrated the feasibility of TT10-ASCT as consolidation for patients in CR/PR/SD following two cycles of R-MA (rituximab, HD-MTX, HD-AraC). Rituximab/busulfan/thiotepa

Study	*N*	Inclusion criteria	Induction	Consolidation	CR rate post-induction	PFS/OS	TRM
IELSG32 (Phase II randomised; two randomisations) *NCT01011920*	219	18–70 years of age ECOG score ≤3 if ≤65 years ECOG score ≤2 if 66-70 years	4 cycles, randomised 1:1:1 of one of the following: **Group A:** MA **Group B:** R-MA **Group C:** MATRix	Patients in CR/PR randomised 1:1 (post induction) to one of the following: **Group D:** WBRT (36Gy if in CR; +9Gy tumour boost if in PR) **Group E:** BCNU/TT ASCT	CR rate post 4 cycles of MATRix: 49% (statistically superior to other arms)	Statistically superior 7-year PFS (52%, 95% CI 47-57) and OS (56%, 95% CI 52–60) observed for MATRix induction No significant difference PFS and OS observed for WBRT and ASCT; quality of life and neurocognitive testing statistically superior for ASCT	MATRix-treated patients (including death during induction or consolidation): 4% Post ASCT (all induction regimens, per-protocol): 5%
PRECIS (Phase II randomised) *NCT00863460*	140	18–60 years of age Any ECOG	2 cycles of R-MBVP followed by 2 cycles of R-AraC (AraC 3g/m^2/day for 2 days each cycle; rituximab 375mg/m^2 once per cycle)	Patients randomised 1:1 (prior to induction) to one of the following, and proceeded regardless of response following induction: **Arm A:** WBRT (40Gy) **Arm B:** Bu/Cy/TT ASCT	CR/CRu rate post R-MBVP/R-AraC induction: 43%	Statistically superior 8-year EFS observed for ASCT (67%, 95% CI 55-83) compared to WBRT (39%,95% CI 27–57) No significant OS difference observed	Post ASCT (per protocol): 11%
IELSG43 "MATRix" (Phase III randomised) *NCT02531841* *Reported in abstract*	346	18–70 years of age Any ECOG if ≤65 years ECOG score ≤2 if 66-70 years	4 cycles of MATRix	Patients in CR/PR randomised 1:1 (post induction) to one of the following: **Arm A:** 2 cycles of R-DeVIC **Arm B:** BCNU/thiotepa ASCT	CR rate following 4 cycles of MATRix: 27%	Despite similar CR rates post consolidation with R-DeVIC and ASCT, statistically superior 3-year outcomes were observed post ASCT in both PFS (79%, 95% CI 71–86) and OS (86%, 95% CI 78–91)	During induction 4% Post ASCT (per protocol): 4%
RTOG 1114 (Phase II randomised) *NCT01399372* *Reported in abstract*	87	≥18 years of age KPS ≥50 (or 30–50 if due to lymphoma)	4 cycles of R-MPV (vincristine omitted in cycles 3 and 4)	Patients randomised 1:1 (prior to induction) to one of the following: **Arm A (chemotherapy only):** 2 cycles of AraC (3g/m2/day for 2 days each cycle) **Arm B (chemo-radiotherapy):** reduced dose WBRT (total dose of 23.4Gy), followed by 2 cycles of AraC with doses as above *Patients in CR/PR/SD proceeded to rdWBRT; those with PD came off study*	Not reported	Statistically superior 2-year PFS demonstrated for chemo-radiotherapy (78%) versus chemotherapy only (54%)	One death from sepsis reported in the chemotherapy arm
MARTA (Phase II, single arm) *DRKS00011932*	51	≥65 years of age ECOG ≤2 (or ≤3 if attributable to lymphoma) Eligible for ASCT	2 cycles of R-MA	Patients in CR/PR/SD proceeded to R/Bu/TT ASCT	CR/CRu in 12% PR in 71% ASCT performed in 36 patients (71%)	1-year PFS 59% (95% CI 44–71%)	NRM during induction (per protocol): 9% NRM post ASCT (per protocol): 5%

Study	*N*	Inclusion criteria	Induction	Consolidation	CR rate post-induction	PFS/OS	TRM
PRIMAIN (Phase II, single arm) *NCT00989352*	107	≥65 years of age Any ECOG	3 cycles of R-MP(L) (lomustine administered to n=69; subsequently removed for the remaining n=38 due to TRM)	No consolidation Maintenance therapy with 6 cycles of procarbazine 100mg for 5 days, repeated every 28 days	CR rate with R-MP: 32%	Overall 2-year PFS and OS were similar with R-MP and R-MPL 2-year PFS with R-MP: 35% (95% CI 19–50) 2-year OS with R-MP: 48% (95% CI 30–65)	R-MPL: 10% R-MP after protocol amendment: 5%
ANOCEF-GOELAMS (Phase II, randomised) *NCT00503594*	95	≥60 years of age KPS ≥40	Patients randomised 1:1 to one of the following: **Arm A:** 3 cycles of MT **Arm B:** 3 cycles of MPV and 1 cycle of AraC (3g/m2/day for 2 days)	No consolidation	Numerically higher CR/CRu rate with MPV-AraC (62%) to MT (45%)	Numerically but not statistically higher 2-year OS with MPV-AraC (58%, 95% CI 43–72%) than MT (39%, 95% CI 26–53)	MT: 10% MPV-AraC: 6%

Table 1. Select clinical trials in newly diagnosed PCNSL[1, 2, 3, 13, 21, 22, 23]; *courtesy of Diva Baggio, MD and Chris P. Fox, MBChB, FRCP, FRCPath, PhD.*

Chemotherapy doses of specific induction regimens:
(R-)MA (IELSG32, MARTA): methotrexate 3.5g/m^2 ; cytarabine 2g/m2 (4 doses per cycle) ± rituximab 375mg/m^2 (2 doses per cycle)
MATRix (IELSG32, IELSG43): methotrexate 3.5g/m^2 ; cytarabine 2g/m2 (4 doses per cycle); thiotepa 30g/m^2 ; rituximab 375mg/m^2 (2 doses per cycle)
R-MBVP (PRECIS): rituximab 375mg/m2; methotrexate 3g/m^2 (2 doses per cycle); etoposide 100mg/m^2; BCNU 100mg/m^2 ; prednisolone 60mg/m^2/day for 5 days
R-MPV (RTOG 1114): rituximab 500mg/m2 (2 doses per cycle); methotrexate 3.5g/m^2 (2 doses per cycle); vincristine 1.4mg/m^2 (dose capped at 2.4mg, 2 doses per cycle; given in cycles 1–2 only); procarbazine 100mg/m^2/day for 7 days
R-MP(L) (PRIMAIN): rituximab 375mg/m^2; methotrexate 3g/m^2 (3 doses per cycle); procarbazine 60mg/m^2/day for 7 days; ± lomustine 110mg/m2 for one dose
MT (ANOCEF-GOELAMS): methotrexate 3.5g/m^2 (2 doses per cycle); temozolomide 150mg/m2/day for 5 days in cycle 1 and 10 days in cycle 2 and 3
MPV (ANOCEF-GOELAMS): methotrexate 3.5g/m^2 (2 doses per cycle); vincristine 1.4mg/m2 (dose capped at 2.8mg, 2 doses per cycle); procarbazine 100mg/m2/day for 7 days

Chemotherapy doses of specific consolidation and conditioning regimens:
R-DeVIC (IELSG43): rituximab 375mg/m^2 ; dexamethasone 40mg (3 doses per cycle) ; etoposide 100mg/m2 (3 doses per cycle), ifosfamide 1500mg/m2 (3 doses per cycle); carboplatin 300mg/m^2
BCNU/TT conditioning (IELSG32, IELSG43): BCNU 400mg/m2 ; thiotepa 20mg/kg divided in 4 doses over 2 days
Bu/Cy/TT conditioning (PRECIS): thiotepa 250mg/m^2/day for 3 days ; busulfan 8mg/kg ; cyclophosphamide 120mg/kg divided in 2 doses over 2 days
R/Bu/TT conditioning (MARTA): rituximab 375mg/m^2 ; busulfan 6.4mg/kg divided in 2 doses over 2 days ; thiotepa 10mg/kg divided in 2 doses over 2 days

Abbreviations: CR: complete remission; **CRu:** unconfirmed complete remission; **PR**: partial remission; **PFS:** progression-free survival ; **OS:** overall survival; **EFS:** event-free survival; **TRM:** treatment-related mortality; **ASCT:** autologous stem cell transplant; **WBRT:** whole brain radiotherapy

(rather than BCNU/TT) conditioning was used based on a pilot study demonstrating tolerability in older patients.[20] Median PFS was 41.1 months (compared to 3.1 months in the 15 patients who did not achieve ASCT), with cumulative non-relapse mortality (NRM) of 14% at 3 years in a per-protocol analysis.

Only two doses of HD-MTX are delivered with the MARTA approach, but this is accompanied by dose-intensive AraC (four 2g/m^2 doses per cycle); relevant to observed toxicities. One-third of patients experienced grade ≥3 infections, including 2 (4%) deaths from infection and a total NRM of 9% during the induction phase. Where fitness for the MARTA approach is unclear, a reasonable initial approach is to deliver an initial cycle of R-HD-MTX to improve ECOG PS and potentially allow intensification with the R-MA regimen for subsequent cycles. This concept is analogous to the currently-recruiting OptiMATe trial for patients ≤70 years.[21] For 'borderline' cases, our practice is to pre-emptively reduce the cytarabine to 2 or 3 doses per cycle whilst increasing the number of cycles delivered to 3–4. However, it is currently unclear whether this empirical approach will confer a similar level of efficacy as the original MARTA protocol.

Patients Unfit for TT-ASCT

For patients considered to be unsuitable for TT-ASCT consolidation, less intensive HD-MTX-based regimens are typically employed as remission induction. Consolidation approaches include 'maintenance' therapy, surveillance only (for those in CR), or WBRT in carefully selected patients with shared decision-making regarding risks and benefits.

The single-arm Phase II PRIMAIN study examined the efficacy of three cycles of R-MP (rituximab, HD-MTX, procarbazine) followed by 6 cycles of oral procarbazine maintenance (100mg for 5 days every 4 weeks; see **Table 1**) in patients ≥65.[22] The oldest enrolled patient in PRIMAIN was 85 (median age 73), and the 2-year OS was 48%, with a median OS 22.6 months. TRM was 2/38 (5%) amongst patients treated with R-MP. A prior protocol version, which included a fourth drug, lomustine (R-MPL), conferred a much higher TRM of 7/69 (10%) and is therefore not recommended.

(R-)MPV-AraC (rituximab, HD-MTX, procarbazine, vincristine, HD-AraC) represents another common induction regimen. The ANOCEF-GOELAMS Phase II randomized study of patients ≥65 years compared two remission induction regimens, either MPV-AraC or MT (methotrexate, temozolomide), without maintenance or consolidation.[23] OS for patients treated with MPV-AraC was numerically higher without statistical significance (2-year OS 58% vs. 39% for MPV-AraC vs. MT, respectively), without differences in grade 3–4 toxicity.

RTOG 1114 was a randomized study of four cycles of R-MPV-AraC without consolidation *versus* R-MPV-AraC followed by reduced-dose WBRT consolidation (rdWBRT; 24.3Gy). The median age was 63 years (range 21–84). The primary study data have not yet been published in full manuscript form, although a superior 2-year PFS in favour of the chemo-radiotherapy arm has been presented in abstract form (78% versus 54%; HR 0.51, p=0.015).[24] Given neurotoxicity concerns associated with combining HD-MTX and WBRT, this approach should only be considered after careful discussion; final study results (including formal cognitive and quality of life assessments) from RTOG 1114 will further inform decision-making.

Patients Unfit for HD-MTX

A minority of patients are unfit for HD-MTX.[11] Options for these patients include palliative WBRT, palliative oral chemotherapy (e.g., temozolomide), or best supportive care. Data from studies of lenalidomide or Bruton's tyrosine kinase inhibitors in the refractory/relapsed setting may support consideration of these agents, which may be off-label within a patient access scheme, if available.

PCNSL in People Living with HIV

HIV-associated PCNSL typically occurs in the setting of severe CD4+ lymphopenia. Tumour cells are invariably positive by Epstein-Barr encoding region (EBER) *in situ* hybridization (ISH).[8,25] In patients with CD4+ lymphopenia, the recommended treatment is six infusions of R-HD-MTX, together with antiretroviral therapy (ART). With this approach, the 5-year OS was 67% in a prospective study.[25] More intensive PCNSL regimens are generally not appropriate in this setting, given toxicity risks and the additional therapeutic effect of ART-associated immune reconstitution. Occasionally, patients with well-controlled HIV, without CD4+ lymphopenia, are diagnosed with EBV-negative PCNSL, for whom treatment should follow the recommendations for immunocompetent individuals.

Concomitant Vitreoretinal Involvement in PCNSL

Vitreoretinal lymphoma is rare, and high-quality evidence to guide treatment is lacking. The systemic agents used in PCNSL have vitreoretinal activity, and in cases of concomitant VRL, a similar treatment paradigm can be applied. Intravitreal chemotherapy injections are not routinely recommended but may have a role in frail patients who are HD-MTX-intolerant. Response in the ocular compartment should be assessed with serial slit-lamp examinations in addition to brain imaging. Consolidation ocular radiotherapy can be considered, with the decision and dose informed by end-of-treatment response.[6,9]

Response Assessment and Surveillance

Response assessment typically follows the International Primary CNS Lymphoma Collaborative Group (IPCG) consensus[26], initially published in 2005 for benchmarking and consistency within clinical trials. With modern PCNSL treatment paradigms, response assessment is recommended every 2 cycles, prior to and following consolidation (after 1–2 months).[16]

The role of surveillance MRI following completion of therapy is less clear. IPCG guidelines recommend surveillance every 3 months for 2 years, 6 months for 3 years, and annually for at least 5 years. Clinical surveillance—including patient education—at these later time points may be sufficient in routine practice.[26] However, MRI surveillance may be particularly important in patients with residual imaging abnormalities on end-of-treatment MRI. Neurocognitive function generally improves with disease response, although it often lags radiological findings. However, late neurotoxicity is observed both following HD-MTX and, more commonly, after radiation-based approaches.[2] Where available, all patients should be referred for formal neuropsychologic assessment as part of a holistic approach to survivorship.

Conclusion

The modern treatment paradigm of PCNSL prioritizes R-HD-MTX-containing chemotherapy for remission induction and is partnered with other CNS-active agents according to patient fitness and institutional protocol experience. Consolidation therapy is key to survival outcomes in PCNSL and TT-ASCT should be pursued in all eligible patients. With this approach, long-term remissions are observed in over half of patients undergoing TT-ASCT. However, of all patients diagnosed with PCNSL, a majority experience relapse, most of whom will die from their disease. This clearly highlights an unmet need in PCNSL, notwithstanding recent therapeutic progress. Ongoing trials are focused on improving the safety and efficacy of first-line regimens. However, a further paradigm shift will require improved prognostication and more sensitive and specific measures of disease activity, which is an area of active investigation. More focus on neurocognitive function and survivorship is also needed and should be embedded as key outcome measures in prospective trials.

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Concise Review of Chronic Myelomonocytic Leukemia in Canada in 2025

Jacqueline Costello, MD

Introduction

Chronic myelomonocytic leukemia (CMML) is a clonal myelodysplastic syndrome/myeloproliferative overlap neoplasm characterized by prominent monocytosis, with a very heterogeneous clinical presentation and an inherent risk of transforming to acute myeloid leukemia (AML). It is relatively rare, and the incidence is poorly defined. A Canadian analysis of a period of 20 years identified 1,440 cases and reported an incidence of 2.45 cases per 1,000,000.[1] Given that it often presents at an advanced age, with a median age of 70–76 years, aggressive therapeutic approaches are limited.

Diagnosis and Differential Diagnosis

CMML is diagnosed and classified according to either the International Consensus Classification (ICC) or the World Health Organization 5th edition (WHO5). The WHO5 CMML diagnostic criteria underwent major revisions, including lowering of the cut-off for absolute monocytosis, adopting of two new subtypes, and eliminating of CMML-0. The ICC diagnostic criteria also eliminated the CMML-0 category.

Monocytosis is characterized as a 3-month peripheral blood monocytosis with a notable decrease from previous to ≥0.5×10^9/L or relative monocytosis of ≥10% of leukocyte counts, consistent bone marrow morphology, <20% bone marrow or peripheral blasts and cytogenetic or molecular evidence of clonality.[2]

Two new disease subtypes with prominent clinical and genetic features were included based on white blood cell (WBC) count, myelodysplastic CMML (MD-CMML) with a WBC count of <13 × 10^9 and myeloproliferative CMML (MP-CMML) with a WBC count of >13×10^9 cells.[2] Two further categories of a) CMML-1 (<5% peripheral blood (PB) blasts, including promonocytes and <10% bone marrow (BM) blasts) and (b) CMML-2 (5%–19% PB blasts, including promonocytes and 10%–19% BM blasts and/or the presence of any Auer rods) remain. Additionally, therapy-related CMML (t-CMML) cases have been described (10% of all CMML cases), and, like their myelodysplastic syndromes (MDS) counterparts, have poorer overall survival and response to systemic therapies.

Variable	ICC	5th edition of the WHO Classification
Absolute monocyte count	• AMC ≥ 0.5 × 10^9/L, with monocytes being ≥10% of the WBC differential	• [b]AMC 20.5 × 10^9/L, with monocytes being >10% of the WBC differential
Cytopenias	• MDS-defining cytopenias	• Not specified
Clonality	• Abnormal karyotype, or myeloid driver mutations with a variant allele fraction >10% • Without a clonal marker the AMC ≥ 1.0 × 10^9/L, along with 25% BM blasts, or BM dysplasia, or an abnormal immunophenotype	• [c]Abnormal karyotype and/or presence of a myeloid driver mutation
CMML categorization	• [a]CMML-1: <5% PB blasts and <10% BM blasts • CMML-2: 5%-19% PB blasts and 10%-19% BM blasts, or the presence of Auer rods • WBC < 13 × 10^9/L-MD-CMML • WBC > 13 × 10^9/L-MP-CMML	• [a]CMML-1: <5% PB blasts and <10% BM blasts • CMML-2: 5%–19% PB blasts and 10%–19% BM blasts, or the presence of Auer rods • WBC <13 × 10^9/L-MD-CMML • WBC >13 × 10^9/L-MP-CMML
Bone marrow aspirate and biopsy	• Hypercellular marrows with increased BM monocytosis. No features of AML or MPN • <20% blasts	• [c]Dysplasia present in ≥1 cell lineage • [b]<20% blasts
Monocyte repartition-based flow cytometry	• Not included	• [c]Presence of classical monocytes (M01) >94%
Exclusionary criteria	• *BCR-ABL1* • Myeloid/lymphoid neoplasms with tyrosine kinase fusions	• [b]*BCR-ABL1* • MPN • Myeloid/lymphoid neoplasms with tyrosine kinase fusions

Table 1. International Consensus Classification and the 5th edition of the World Health Organization Classification systems for diagnosis of chronic myelomonocytic leukemia (CMML); *adapted from Khoury JD, et al., 2022*.

[a]In CMML promonocytes are considered blast equivalents and should be included in the blast count.
[b]Prerequisite criteria by the WHO for a diagnosis of CMML
[c]Supportive criteria for diagnosis of CMML. If the AMC ≥ 1 × 10^9/L, all prerequisite criteria and one supportive criterion should be present. If AMC > 0.5 × 10^9/L, then all prerequisite criteria and the presence of a clonal marker and BM dysplasia should be present. For the ICC cases without evidence of clonality, AMC 1.0 × 10^9/L and >10% of the WBC, and increased blasts (including promonocytes), or morphologic dysplasia, or an abnormal immunophenotype consistent with CMML would be required for the diagnosis of CMML. For cases lacking bone marrow findings of CMML, a diagnosis of CMUS (clonal monocytosis of undetermined significance) could be considered. If cytopenia is present, a diagnosis of CCMUS (clonal cytopenias with monocytosis of undetermined significance) could be entertained. In these diagnostic settings, however, an alternative cause for the observed monocytosis would have to be excluded based on appropriate clinicopathologic correlations. Myeloid and lymphoid neoplasms with tyrosine kinase fusions include recurrent abnormalities involving the following genes and rearrangements; *PDGFRA, PDGFRB, FGFR1, JAK2, FLT3, and ETV6-ABL1*.

Abbreviations: AMC: absolute monocyte count; **AML:** acute myeloid leukemia; **BM:** bone marrow; **ICC:** International Consensus Classification; **MDS:** myelodysplastic syndrome; **MPN:** myeloproliferative neoplasm; **WBC:** white blood cell count; **WHO**: World Health Organization.

Distinguishing CMML from other causes of monocytosis can be challenging, but certain findings can help support or exclude the diagnosis, including the flow cytometry immunophenotype (increased CD14+CD16- monocytes); exclusive genetic abnormalities, including *BCR::ABL1, PDGFRA-/B-, FGFR1*-rearrangement, and PCM1::JAK2; and patient having a prior myeloproliferative neoplasm (MPN). Dysplasia is generally more subtle and typically seen in <10% of mononuclear cells. CMML also often manifests more proliferative features, such as splenomegaly, leukocytosis, and constitutional symptoms.

BCR-ABL1-positive chronic myelogenous leukemia (CML) can present with monocytosis, especially in the presence of the p190 BCR-ABL1 fusion transcript, and should be excluded. The presence of *FLT3-ITD* or *NPM1* mutations may suggest the alternative diagnosis of AML, which masquerades initially as CMML.[3] In addition, the possibility of clonal hematopoiesis of indeterminate potential (CHIP) should be considered for cases with single gene mutations and a low variant allele frequency (VAF), particularly when mutations involve *DNMT3A, TET2*, or *ASXL1*.[2]

Molecular Pathogenesis

CMML often arises in the background of clonal hematopoiesis, with subsequent acquired mutations. Cytogenetic abnormalities are found in 30% of patients, of which trisomy 8 and various abnormalities of chromosome 7 are the most prevalent.[4] Approximately 90% of patients will have characteristic somatic mutations involving epigenetic regulation (*EZH2, ASXL1*, and *UTX TET2, DNMT3A, IDH1*, and *IDH2*), the spliceosome (*SF3B1, SRSF2, U2AF1, ZRSR2, PRPF8*), and signal transduction genes (*JAK2, KRAS, NRAS, CBL, PTPN11, NF1*, and *FLT3*).[5] Of these, mutations involving *TET2* (60%), *SRSF2* (50%), *ASXL1* (40%), and the oncogenic RAS pathway (30%) are the most frequent. In particular, the combination of *TET2* and *SRSF2* mutations is frequently observed in CMML, and has been shown to be highly specific for myeloid neoplasm with monocytosis.[6] VAF, nucleic acid, and amino acid changes of all likely pathogenic variants are important, as these can affect the prognostic relevance; missense mutations in ASXL1 do not seem to carry the same prognostic relevance as nonsense and frameshift mutations.

Risk Stratification

Several risk models developed for MDS to identify high-risk patients have also been used to risk stratify CMML, such as the International Prognostic Scoring System (IPSS) and its derivatives. Consensus for one widely used system has not been established, which is likely due to the relatively small number of patients and the heterogeneity between patients with CMML. However, three more recent models have taken more specific CMML features into account. The CMML-specific prognostic scoring system (CPSS-Mol) stratifies patients with CMML into four risk categories: low (0 risk factors), intermediate-1 (1 risk factor), intermediate-2 (2–3 risk factors), and high (≥4 risk factors) risk, with median OS of not reached, 64, 37, and 18 months, and 4-year leukemic transformation rates of 0%, 3%, 21%, and 48%, respectively.[7]

The Mayo Molecular Model (MMM) includes *ASXL1* mutations, absolute monocytes (AMC) $>10 \times 10^9$/L, hemoglobin (Hb) <10 g/dL, platelets $<100 \times 10^9$/L, and circulating immature myeloid cells (IMC), which were independently predictive of shorter OS. In this prognostic model, high (≥3 risk factors), intermediate-2 (2 risk factors), intermediate-1 (one risk factor), and low (no risk factors) risk categories have median OS of 16, 31, 59, and 97 months, respectively.[3] In a recent update of the model, the revised Mayo Molecular Model (MMMv2), *DNMT3A* is recognized as the most unfavourable and *PHF6* as the most favourable mutation, and this update also includes the important indicators of red blood cell transfusion need and leukocytosis (≥13 × 10^9/L).

The Groupe Français des Myélodysplasies (GFM) risk model demonstrated an adverse prognostic effect for *ASXL1*, age >65 years, WBC $>15 \times 10^9$/L, platelet count $<100 \times 10^9$/L, and Hb <10 g/dL in females and <11 g/dL in males. The GFM model assigns three adverse points for WBC $>15 \times 10^9$/L and two adverse points for each one of the other risk factors, resulting in a three-tiered risk stratification: low (0–4 points), intermediate (5–7), and high (8–12), with respective median OS of 56, 27.4, and 9.2 months.[8]

Risk-Adapted Therapy

Pretreatment evaluation of a patient with CMML to identify disease-associated symptoms and evaluate their medical fitness is crucial for goals of care discussions regarding whether systemic therapies are recommended. Many patients with CMML who do not have significant

cytopenia or symptomatology may be observed without treatment. No clear thresholds exist for the initiation of therapy, but like for MDS, Hb levels <100 g/L and platelets <30×10^9/L often trigger therapy. There is no demonstrated WBC threshold to start treatment in the case of myeloproliferation. Therapy is also often incited in the case of symptomatic splenomegaly, extramedullary disease, or constitutional symptoms.

Treatment options for CMML have evolved over the last three decades from using toxic chemotherapy to DNA methyltransferase inhibitors (DNMTi)/ hypomethylating agents (HMA). The approval of these drugs in Canada was based on the inclusion of patients with CMML in MDS-predominant trials.[4,13] When selecting therapy for patients with CMML considered "unfit", it is important to select a therapy that targets the nature of the symptoms (i.e., cytopenic patients may have a better response with HMAs), and myeloproliferative patients may benefit from cytoreduction (hydroxyurea).

HMAs

HMAs remain the only approved novel drugs for the management of CMML in Canada and are associated with overall response rates (ORR) of 40%–50% and true complete remission (CR) rates of <20%.[9] No randomized trial has directly compared azacitidine versus decitabine for CMML. Predictors of response to HMA have not been established, but there are some suggestions that the *ASXL1*^{WT}/*TET2*^{MT} genotype might be the most predictive.[10] Several studies indicate that MP-CMML still has a shorter survival than MD-CMML when treated with HMAs.[9,11] However, there is no obvious trend correlating response to HMAs in CMML with the extent of myeloproliferation.[9]

5-Azacitidine

The pivotal North American CALGB 9221 study (n = 191) only included 14 patients with CMML, and the European AZA-001 study only included 11 patients with CMML (all MD-CMML).[12,13] The ORR for these studies was approximately 40%, but complete and sustained responses were found in fewer than 20% of patients.

Cedazuridine/Decitabine

The efficacy of single-agent intravenous decitabine has been assessed in a handful of trials with few patients, and ORRs were detected to be between 25–40%.[14] Also in trials investigating the combination oral therapy cedazuridine and a cytidine deaminase (CDA) inhibitor, the MDS-focused Phase 3 Ascertain and the Phase 2 ASTX727 study[15], very few patients with CMML patients were included. In these studies, patients with CMML were found to have CR rates of <20% and a mean duration of response of about 9 months. However, close to 50% of patients achieved platelet and/or red blood cell independence for the duration of response.

Cytoreductive Therapy

Hydroxyurea (Hydrea)

Hydroxyurea has been used to offset splenomegaly and other constitutional symptoms of CMML with the goal of achieving a balance between reducing symptoms and exacerbating neutropenia, anemia, and thrombocytopenia. It is not clear whether CMML-MP responds better to HMAs or hydroxyurea. The Phase 3 DACOTA study showed that compared with hydroxyurea, front-line treatment with decitabine did not improve event-free survival in patients with advanced myeloproliferative CMML. However, decitabine was associated with a lower risk of CMML progression or transformation to acute leukemia in this study, but the trade-off with this therapy are the Grade ≥3 infections in 33% of patients treated with decitabine, which is lower at 18% in those treated with hydroxyurea, and hospitalization occurred in 60% and 40%, respectively.[6] Other agents, such as etoposide and cytarabine, have been used, but have not been shown to be more effective than hydroxyurea.[8]

Allogeneic Stem Cell Transplant

Allogeneic stem cell transplantation (alloSCT) remains the only curative therapy but is only an option for a fraction of patients due to advanced median age and co-morbidities excluding them. OS for patients with CMML ranges from 30–40% at 5 years after alloSCT, owing to relapses and non-relapse-related mortality, such as graft vs. host disease (GvHD) and infection.[16] Pre-transplantation treatment should be designed to maximize bone marrow responses while minimizing toxicity, and should be selected using the characteristics of the disease as well as the comorbidities of the patient.

A report on the outcomes of alloSCT after azacitidine-based low-intensity treatment in 277 high-risk patients with MDS and CMML, showed similar outcomes to historical controls

who received transplantation after intensive chemotherapy. This has led to the wide use of HMAs pre-transplant for lower blast burden.[11] HMA may also be considered in patients with mutated *TET2* and wild-type *ASXL1* as they appear to have higher response rates to HMAs, including in CMML.[6]

Response to Therapy

The MDS/MPN international working group (IWG) formulated specific disease response criteria to include CMML. Response to therapy can be judged based on clinical benefit, hematologic response, resolution of hepatosplenomegaly/extramedullary disease, morphologic response in bone marrow, and improvement of quality of life.[17]

Relapsed Disease

Unfortunately, based on clinical experience, for relapsing patients with progressive disease who have previously been exposed to HMA or received an alloSCT, prognosis is poor, with survival measured in weeks to months. Patients with CMML at this stage are strongly encouraged to enter clinical trials.

Supportive Care

Erythropoietin-stimulating agents, prophylactic antibiotics, and other supportive care have not been widely studied in CMML, but it has been demonstrated to benefit some MDS populations.[18]

Conclusion And Future Directions

CMML is a rare MDS/MPN crossover neoplasm with heterogeneous clinical outcomes, and the disease is often underrepresented in trials. However, over the last decade, epigenetics and pathogenesis of the disease have gained traction in separating it from MDS, which has resulted in trials with more specific novel therapies. Novel targets, including RAS, BCL2, JAK-STAT, and SRSF2, as well as bispecific T-cell engagers, have been explored with limited to modest success in small numbers of patients in early phase trials.[19,20] A PLK1 inhibitor, onvansertib, is currently being tested in hydroxyurea and/or HMA-relapsed, refractory, or intolerant patients (NCT05549661). Similarly, given that high-dose intravenous ascorbic acid can enhance unmutated *TET2* and *TET3* catalytic activity, there is a pilot study ongoing assessing high-dose intravenous ascorbic acid with decitabine in newly diagnosed CMML (NCT03418038). Additionally, EP31670 is a novel oral dual BRD4/p300 inhibitor that is being tested in *ASXL1* mutant relapsed/refractory CMML (NCT05488548). Given the high frequency of spliceosome mutations in CMML (*SRSF2*), several spliceosome inhibitors are also being explored. For these patients, excellent goals of care discussions are essential, and it is recommended to continue encouraging enrollment in clinical trials.

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