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CANADIAN HEMATOLOGY TODAY

**FRONTLINE MANAGEMENT OF TRANSPLANT
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MYELOMA (TINDMM) IN CANADA**

**Christopher Venner, MD
Julia Varghese, MD**

**MANAGEMENT OF LIMITED STAGE HODGKIN
LYMPHOMA**

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REGIMENS FOR ACUTE MYELOID LEUKEMIA:
CLINICAL PEARLS FOR A NEW STANDARD OF
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**TYROSINE KINASE INHIBITORS FOR THE
FRONTLINE MANAGEMENT OF CML: AN
OVERVIEW**

Dennis Dong Hwan Kim, MD

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FRONTLINE MANAGEMENT OF TRANSPLANT INELIGIBLE NEWLY DIAGNOSED MULTIPLE MYELOMA (TINDMM) IN CANADA

Introduction

Multiple myeloma (MM) is a hematologic malignancy characterized by clonal proliferation of plasma cells in the bone marrow leading to end organ dysfunction including hypercalcemia, anemia, renal dysfunction, and/or bony lytic lesions.¹ The median age of diagnosis is 69 years of age with approximately one-third of newly diagnosed patients presenting over age 75.² Therefore, a significant portion of patients presenting with newly diagnosed MM are considered ineligible for transplant due to chronological age, comorbidities or frailty. This category represents a largely heterogeneous group of patients. With options for frontline management rapidly changing, practitioners must consider the optimal treatment modality.

Patient Eligibility for Autologous Stem Cell Transplant

In younger, fit populations, autologous stem cell transplant (ASCT) remains the standard of care and multiple trials have demonstrated a consistent progression-free survival (PFS) benefit.^{3,4} However, most of these studies excluded patients who were >65 years of age. The Myeloma XI trial attempted to address this gap with a subgroup analysis of patients up to age 75. In this trial, the transplant decision was left to the discretion of the clinician. Older patients who underwent ASCT were found to have an improvement in PFS (HR=0.41, P<0.0001), as well as OS (HR=0.51, P<0.0001) compared to their age-matched cohort that did not.⁵ Patients age 65-69 had a PFS of 40 months, and a PFS of 34.4 was seen in those aged 70-75.⁵ These results are similar to those of newer non-ASCT based therapies, thus calling into question the role of ASCT in these age groups.^{6,7}

There is no universally accepted age cut-off for transplant eligibility. The European guidelines recommend an age cut-off of 70 years of age for transplant eligibility,⁸

whereas there is no formal age cut-off in the National Comprehensive Cancer Network guidelines.⁹ Knowing this, the majority of Canadian clinicians will assess therapeutic options based on performance status. Several tools have been validated for use in stratifying patients into “fit” and “frail” categories, including the International Myeloma Working Group (IMWG) frailty assessment and the Revised Myeloma comorbidity index.^{10,11} These tools are helpful in assessing transplant eligibility as well as how patients may tolerate chemotherapy in general. Regardless of transplant status, the objective of therapy is to achieve the best possible response with minimal toxicities and to maximize disease control in the long term.

Treatment modalities for transplant ineligible newly diagnosed multiple myeloma

As per the most recent Canadian Agency for Drugs and Technologies in Health (CADTH) review, the six regimens that are currently approved and funded for front-line treatment for transplant ineligible newly diagnosed multiple myeloma (TINDMM) patients in Canada appear below and are further described in **Table 1**.¹²

- Daratumumab, lenalidomide, dexamethasone (DRd)
- Bortezomib, lenalidomide, dexamethasone (VRd)
- Lenalidomide, dexamethasone (Rd)
- Daratumumab, cyclophosphamide, bortezomib, dexamethasone (Dara+CyBorD)
- Daratumumab, bortezomib, melphalan, prednisone (Dara+VMP)
- Cyclophosphamide, bortezomib, dexamethasone (CyBorD)

Trial	Therapy	Number of patients	mPFS	mOS
MAIA ¹³ (DRd)	DRd vs Rd	737	61.9 months vs 34.4 months with Rd	66.7% at 60 months vs 53.7%
ALCYONE ¹⁴ (Dara+VMP)	DVMP vs VMP	706	36.4 months vs 19.3 months with VMP	78% at 36 months vs 67.9%
SWOG-S0777 ⁶ (VRd)	VRd vs Rd	525	43 months vs 30 months with Rd	75 months vs 64 months
FIRST ¹⁵ (Rd)	Rd vs MPT	1623	25.5 months vs 21.2 months with MPT	70% at 3 years vs 62% with MPT
VISTA ¹⁶ (VMP)	VMP vs MP	682	19.9 months (time to progression) vs 13.1 months with MP	Not reported

Table 1. Comparison of PFS and OS of the current CADTH-approved frontline regimens for transplant ineligible patients based on Phase III trial data. mPFS= median Progression Free Survival; mOS= median Overall Survival



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Although CyBorD has never been studied in a phase III clinical trial, it is a widely used regimen in Canada. It was adopted following a phase II trial in transplant eligible patients which demonstrated its efficacy as an induction regimen.¹⁷ Given the efficacy and tolerability, this regimen was moved into the transplant ineligible population with similar outcomes compared with VMP.^{18,19}

When reviewing the real-world Canadian data from the Canadian Myeloma Research Group (CMRG) of various frontline regimens there appears to be an increased PFS benefit with lenalidomide-containing regimens, particularly the triplet regimen VRD.¹⁹ Data from the CMRG database examining patients from 2007-2021 demonstrated a median PFS for VMP of 23.5 months (n=460); 22.9 months for CyBorD (n=932); 34 months for RD (n=472); and a median PFS not yet reached for VRD (n=115) at the time of analysis.¹⁹

These results are comparable to the recent trial data that led to their respective approvals, such as data from the FIRST trial which compared continuous Rd to MPT and demonstrated improved PFS (25.5 months vs 21 months) as well as OS.¹⁵ It is also comparable to the control arms of other recent trials where Rd was the backbone.^{6,13,20} This benefit was further improved with the addition of bortezomib to Rd in the SWOG S0777 trial which demonstrated a further increase in PFS (43 vs 30 months) and median OS (75 vs 64 months) in the study arm.⁶ Due to tolerability concerns of lenalidomide, as well as twice weekly bortezomib, a phase II trial reviewing the efficacy of “RVD-lite” in 53 transplant ineligible patients (median age 73) was conducted. This regimen examined a lower dose of lenalidomide (15 mg) and weekly bortezomib. The median PFS with this regimen was 35.1 months; the median OS was not reached after a median follow-up of 30 months. The regimen was well tolerated.²¹ The rates of peripheral neuropathy were 62%; however only one patient (2%) had peripheral neuropathy recorded as grade 3 or higher. The treatment discontinuation rate due to side effects was low, at 4%.²² This clinical trial demonstrated the efficacy and tolerability of the modified RVD regimen in the elderly non-transplant population, even at reduced doses.

More recent clinical studies have evaluated anti-CD38 monoclonal antibodies in combination with gold standard therapies. The ALCYONE trial reported a benefit for Dara + VMP compared to VMP in both PFS and OS (**Table 1**).¹⁴ The most promising data, however, has been demonstrated with DRd from the MAIA study.¹³ This phase 3 trial comparing DRd to Rd demonstrated superior PFS (mPFS 61.9 vs 31.9 months). Recent follow-up data of the MAIA study has shown a higher proportion of patients achieving minimal residual disease (MRD) negativity status (32.1% vs 11.1%; $P<0.0001$), with a significant portion of patients achieving sustained MRD negativity for >18 months at a median follow-up of 64.5 months

(16.8% vs 3.3 %; $P<0.0001$).¹³ This is notable as numerous clinical studies have demonstrated improved outcomes for patients who achieve a sustained MRD status.²² In the MAIA trial, OS was improved overall but also specifically for patients who achieved an MRD negative status compared to those who were MRD positive regardless of the arm. An increased number of DRd patients achieving MRD negativity may explain the improved survival endpoints with the monoclonal antibody (mAb)- containing triplet.

The benefit of DRd over Rd was demonstrated throughout the subgroup analysis.^{7,23} This included patients with one high-risk cytogenetic abnormality (HRCA) (PFS 61.4 vs 31.2 months); age >75 years (54.3 vs 31.4 months); International Staging System (ISS) Stage III disease (42.4 vs 24.2 months); renal insufficiency (56.7 vs 29.7 months); and extramedullary plasmacytomas (57.5 vs 19.4 months). No significant difference was reported between patients with two or more HRCA (24.9 vs 24 months) although there were small numbers in each group making it difficult to draw conclusions from this data.²³ Interestingly, for patients aged 70-75 and 65-70, the median PFS was 61.9 months and not yet reached, respectively.⁷ This is similar, if not longer, than what can be achieved with non-mAb transplant regimens used in Canada based on both prospective and real-world data.^{5,24}

In the frailty subgroup analysis of MAIA, 341 patients were deemed frail (172 in the DRd arm vs 169 in the Rd arm). After a median follow-up of 36.4 months, the non-frail patients (n=396) had longer PFS vs the frail patients (n=341).²⁵ However, regardless of frailty, the PFS benefit of DRd persisted compared to that of Rd (mPFS not reached vs 30.4 months; $P=0.003$). Not surprisingly, the rates of treatment emergent adverse events (TEAE) were higher in the frail population vs that of the fit. The primary grade 3/4 TEAE for frail patients in the DRd arm was neutropenia ([DRd] 57.7% vs [Rd] 33.1%). The most serious non-hematologic TEAE was infections (primarily pneumonia/upper respiratory tract infection [URTIs]) and was higher for the DRd arm (41.7% vs 27.7%). However, DRd was better tolerated overall and fewer of the frail patients discontinued DRd in comparison to Rd (45.3% vs 67.5%).²⁵

Dexamethasone toxicity can be a limiting factor for many patients, and the efficacy of a dexamethasone sparing regimen was recently evaluated. In this clinical trial, 295 elderly patients (median age of 81 years) were randomized to daratumumab, lenalidomide and dexamethasone (administered weekly for 8 weeks, then discontinued) or lenalidomide and weekly dexamethasone 20 mg.²⁶ The overall response rates were higher for DR vs Rd (89% vs 77%; $P=0.025$). Patients in the DR arm had higher rates of neutropenia (44% vs 15%; $P<0.001$) but similar rates of grade 3 infections (13% vs 17%; $P=0.38$) and similar rates of discontinuation due to adverse events (AEs) (13% vs 16%; $P=0.64$).²⁶

While frontline DRd is already improving patient outcomes, several new treatment approaches currently being evaluated in clinical trials may result in further future improvement. Anti-CD38 monoclonal antibody-containing quadruplet regimens are currently being evaluated in TINDMM, with the objective of improving the depth and duration of response. T-cell redirecting therapies such as B-cell maturation antigen (BCMA)-targeted chimeric antigen receptor (CAR-T) and bispecific T-cell engagers (BiTEs) are also being evaluated in this population in the frontline setting.

Summary

When reviewing the status of TINDMM patients in Canada treated between 2007 and 2018, prior to the availability of daratumumab, the median OS was 54 months.²⁷ Incremental gains have been achieved with novel regimens such as RVd; however, the most significant advances have been reported with the anti-CD38 mAbs. In particular, the promising data with DRd demonstrates a median PFS of 61.9 months¹³ exceeding the median OS with regimens from the previous era. Furthermore, DRd is well-tolerated and provides benefit regardless of age, cytogenetic risk, frailty or renal function.

Although there are several options approved for use by CADTH in the frontline setting for transplant ineligible patients, DRd remains the most broadly applicable regimen for frontline therapy in TINDMM and will serve as the backbone upon which future advances will be built.

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CONTROVERSIES AND CURRENT PRACTICES IN CNS RELAPSE OF DIFFUSE LARGE B-CELL LYMPHOMA

Introduction

Central nervous system (CNS) relapse is an uncommon complication of diffuse large B-cell lymphoma (DLBCL), occurring in approximately 3-5% of patients and at a median timepoint of 6-9 months from diagnosis.¹ Approximately half of these cases present as isolated CNS relapse caused by occult seeding of the CNS early in the disease course, while the remaining cases occur in the context of concurrent systemic relapse.² The median survival after CNS relapse is only 4-6 months,³ highlighting the unmet need to identify effective prophylaxis and management strategies. This article provides an overview of current controversies and optimal strategies for prognosticating, preventing, and treating CNS relapse in patients with DLBCL.

Can CNS relapse be prognosticated?

The most well-established risk model for prognosticating CNS relapse in DLBCL is the CNS-IPI score, which is comprised of the 5 risk factors of the International Prognostic Index (age >60 years, Eastern Cooperative Oncology Group [ECOG] performance status >1, elevated lactate dehydrogenase [LDH], >1 extranodal site, stage III/IV) with the addition of kidney or adrenal involvement⁴. The 12-23% of patients with 4-6 risk factors have a 10-12% incidence of CNS relapse, which is considered to be high risk. Unfortunately, almost half of the patients who experience CNS relapse do not have a high-risk CNS-IPI score at diagnosis, and almost 90% of patients with a high-risk CNS-IPI score do not develop CNS relapse. There is also significant heterogeneity within the high-risk CNS-IPI group, with the CNS relapse risk ranging from 7% for a score of 4 to 32% for a score of 6.⁴ Incorporation of the molecular cell-of-origin into the CNS-IPI model may improve prognostic capability, as patients with a high CNS-IPI score and activated B-cell subtype have a 15% risk of CNS relapse.⁵ Prior reports have suggested that MYC and BCL2 protein over-expression or gene rearrangements are also associated with >10% risk of CNS relapse.¹ However, a more recent study found that the 2-year cumulative incidence of CNS relapse in patients with *de novo* double hit lymphoma treated with curative intent was only 6% for those with DLBCL morphology and 11% for high grade morphology.⁶ In addition, several clinical or anatomic risk factors are associated with a >10-20% risk of CNS relapse, including the presence of multiple extranodal sites, markedly elevated LDH, and testicular, uterine, or breast lymphoma.¹ These risk factors also have limited sensitivity and specificity for prognosticating CNS relapse, and further work is needed to identify a group of patients with DLBCL at uniformly high risk of CNS relapse.

Is there a role for CNS prophylaxis in DLBCL?

CNS prophylaxis remains an area of considerable controversy despite limited evidence of benefit. Interestingly, the only

agent proven in a randomized trial to reduce the risk of CNS relapse is rituximab,⁷ and the risk of CNS relapse has fallen to 3% in the rituximab era likely owing to improved control of systemic disease.⁸ While intrathecal (IT) chemotherapy has been a commonly used prophylactic approach in DLBCL, it does not penetrate the brain parenchyma where the majority of CNS relapses occur. In addition, a systematic review examining 7,357 rituximab/obinutuzumab-exposed patients from 14 studies concluded there is no evidence that IT chemotherapy reduces the risk of CNS relapse in DLBCL.⁹

Intravenous high-dose methotrexate (HD-MTX) does penetrate the blood-brain barrier and has become widely used as a prophylaxis agent in DLBCL. However, it is a resource-intensive therapy that typically requires 4-5 days of hospitalization with careful monitoring and supportive care to prevent toxicities including mucositis, renal or hepatic dysfunction, and myelosuppression. As a result, HD-MTX may not be feasible for many patients, including those with older age or medical comorbidities. Several small studies suggested that HD-MTX prophylaxis may be associated with lower risks of CNS relapse.^{10,11,12} However, these studies must be interpreted cautiously given their retrospective design, small sample size, lack of concurrent controls, and/or obvious selection biases such as using HD-MTX only for fit patients who achieved a complete response with R-CHOP. Despite the limited evidence, international guidelines adopted the recommendation that HD-MTX prophylaxis be administered to patients with DLBCL at high risk of CNS relapse.^{13,14} Importantly, over the past 2 years, several groups have reported their experience with HD-MTX prophylaxis and consistently concluded that this practice does not appear to reduce the risk of CNS relapse.^{15,16,17,18,19} In the largest of these studies which included almost 2,300 high-risk patients, the use of HD-MTX was not associated with a significant reduction in the risk of CNS relapse overall nor in any high-risk subgroup.¹⁸ In a separate retrospective study of 1,384 patients, CNS relapse rates remained as high as 9% despite the uniform administration of HD-MTX prophylaxis, casting further doubt on the efficacy of this intervention.¹⁹ Importantly, the intercalation of HD-MTX between R-CHOP cycles was associated with a 20% risk of R-CHOP treatment delays and a trend to increased treatment-related mortality.¹⁹ This is of particular concern given that patients at risk of CNS relapse are at even greater risk of systemic disease progression, and the safe and timely administration of R-CHOP is paramount.

Taken in totality, the available data is clear that there is no proven role for the routine administration of CNS prophylaxis in DLBCL. A matter of ongoing debate is whether there are any high-risk subgroups who might still benefit from

CNS prophylaxis. For example, a phase II trial of 38 patients with intravascular large B-cell lymphoma found that the combination of R-CHOP and HD-MTX resulted in a CNS relapse risk of 3%, which is remarkably low for this high-risk subtype of DLBCL.²⁰ Another subgroup with a particularly high risk of CNS relapse are patients with primary testicular lymphoma, for which prophylactic HD-MTX is often recommended based on a phase II trial of 54 patients reporting a 5-year CNS relapse rate of 0%.²¹ However, there are insufficient data to definitively confirm a benefit of HD-MTX prophylaxis even in these high-risk subgroups, and the potential risks must be weighed against the lack of proven benefit in discussion with patients. Specifically, if a physician chooses to treat a patient with HD-MTX prophylaxis despite the unproven benefit for any subgroup of patients with DLBCL, then it should be administered after completion of R-CHOP to reduce the risks of toxicity and optimize relative dose intensity of the more important R-CHOP treatment.¹⁹

How should CNS relapse be treated?

CNS relapse is associated with a poor prognosis and there are no randomized controlled trials to guide management. Conventional chemotherapy with CNS-penetrating drugs such as HD-MTX and cytarabine are frequently used, but most responses tend to be short-lived.²² As a result, consolidation with thiotepa-based high-dose chemotherapy and autologous stem cell transplantation (ASCT) should be considered based on the durable remissions demonstrated in several prospective studies.^{23,24,25} In the phase II MARIETTA trial, 75 patients with secondary CNS lymphoma (SCNSL) received MATRix and R-ICE induction followed by thiotepa/BCNU conditioning and ASCT, yielding a 2-year progression-free survival (PFS) rate of 46% for all patients and 83% among those who received ASCT in an exploratory analysis.²⁵ In a recently published series from Alberta, the 5-year PFS was 53% for 62 consecutive patients with SCNSL intended for ASCT, and 62% for the 52 patients who received high-dose thiotepa, busulfan, melphalan, rituximab conditioning and ASCT.²⁶ Of note, the outcomes with ASCT are better for patients with isolated CNS relapse compared to those with concurrent CNS and systemic disease.^{26,27}

Alternative treatments are needed for patients who are ineligible for ASCT due to poor medical fitness or chemo-refractory disease. Preliminary evidence suggests that chimeric antigen receptor (CAR) T-cell therapy achieves encouraging response rates in CNS lymphoma with comparable rates of cytokine release syndrome and neurotoxicity as with systemic lymphoma, although larger studies with longer follow-up are needed to confirm the durability of responses.²⁸ Targeted agents such as Bruton's tyrosine kinase (BTK) inhibitors or lenalidomide also have established activity in CNS lymphoma.^{29,30} Palliative whole-brain radiation therapy (WBRT) may also be considered but is associated with risks of neurotoxicity and poor long term survival.³¹

What does the future hold for CNS relapse?

Given the lack of demonstrable benefit and the potential toxicities of HD-MTX, novel CNS prophylaxis strategies are needed. Targeted agents such as the BTK inhibitor ibrutinib or the immunomodulator lenalidomide do penetrate the blood-brain barrier, but neither has been confirmed to be beneficial in DLBCL and no adequately powered studies have been performed to evaluate their role as agents for CNS prophylaxis.^{32,33} Surprisingly, a post-hoc analysis of one randomized trial found that maintenance lenalidomide after R-CHOP was associated with increased risks of CNS relapse.³⁴ More promising strategies under investigation include the incorporation of molecular tumor profiling or cerebrospinal fluid circulating tumor DNA (ctDNA) analysis to identify patients at very high risk of CNS relapse who might benefit from prophylaxis, although confirmation in larger studies is needed.^{35,36,37} Finally, it is also hoped that advances in the treatment of DLBCL, including the integration of polatuzumab vedotin into frontline therapy and the use of second-line CAR T-cell therapy, might reduce the risk of CNS relapse by optimizing control of systemic disease.^{38,39,40}

Conclusion

While the optimal strategies for prognosticating and preventing CNS relapse remain controversial, there is growing consensus that prophylactic IT chemotherapy and HD-MTX likely provide no significant benefit for most patients with DLBCL. As the field moves beyond the CNS-IPI score to incorporate novel risk stratification tools including genomic subgrouping and high-sensitivity ctDNA analysis, it is possible that selective targeting of CNS prophylaxis to ultra-high-risk subgroups may prove to be a more effective strategy in the future. In the meantime, clinicians can reassure their patients that the risk of CNS relapse remains low in the rituximab era, and it will hopefully continue to decline as novel therapies emerge to improve systemic disease control. In addition, the early detection of CNS involvement and the timely administration of thiotepa-based ASCT is a promising strategy to overcome the historically poor prognosis of CNS relapse.

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MANAGEMENT OF LIMITED STAGE HODGKIN LYMPHOMA

Introduction

Hodgkin lymphoma (HL) is a lymphoid neoplasm characterized by malignant lymphocytes, known as Reed-Sternberg cells, on a background of non-neoplastic inflammatory cells. Lugano staging¹ (**Table 1**) determines the stage of Hodgkin lymphoma, which, in turn, determines the treatment and prognosis. Limited-stage disease is defined as Stage I and Stage II, which is diagnosed in more than 50% of patients.² Pre-treatment risk stratification, PET-adapted therapy, and combined modality treatment have significantly improved cure rates, making limited-stage HL one of the most curable malignancies.³ In this article, we discuss the current approach to managing limited-stage HL.

Staging and Risk Stratification

Accurate staging and risk assessment are crucial for proper assignment to a risk group and making informed treatment decisions in HL. Lugano classification for the staging of lymphomas includes Stage I to Stage IV (**Table 1**). Patients with Stage I and Stage II are classified as limited or early-stage disease. PET/CT is recommended for initial staging in the National Comprehensive Cancer Network (NCCN) and European Society of Medical Oncology (ESMO) HL guidelines,⁴ and Lugano classification.¹ In a retrospective analysis, PET, in addition to a contrast-enhanced computed tomography (CT) scan, upstaged the disease in up to 25% of patients.⁵ The improved sensitivity and specificity of PET/CT enable the elimination of the initial bone marrow biopsy for patients with normal [18F]FDG uptake in the bone marrow.⁶

Stage I – Involvement of a single lymph node region (I) or a single extra lymphatic organ or site (IE)

Stage II – Involvement of two or more lymph node regions on the same side of the diaphragm alone (II) or with involvement of limited, contiguous extra lymphatic organ or tissue (IIE)

Stage III - Involvement of lymph node regions or lymphoid structures on both sides of the diaphragm; nodes above the diaphragm with spleen involvement

Stage IV - Diffuse or disseminated involvement of 1 or more extranodal organs or tissue beyond that designated “E,” with or without associated lymph node involvement

All cases are subclassified to indicate the absence (A) or presence (B) of the systemic symptoms of significant unexplained fever, night sweats or unexplained weight loss exceeding 10% of body weight during the six months before diagnosis.

Bulky disease: A single nodal mass, in contrast to multiple smaller nodes, of 10 cm or ≥ one-third of the transthoracic diameter at any level of thoracic vertebrae as determined by CT.

Table 1. Lugano classification for staging of lymphomas¹

Patients with limited Stage (I to II) disease are further divided into favourable and unfavourable prognosis categories based on specific clinical features such as age; B symptoms; erythrocyte sedimentation rate (ESR); number of involved sites (the definition of the involved site differs in each group classification); sizeable mediastinal mass; bulky disease; and extranodal disease. Various cooperative research groups have employed differing definitions for favourable and unfavourable prognosis disease (**Table 2**).

German Hodgkin Study Group (GHSg)^{7,8}
Large mediastinal adenopathy (> one-third maximum transverse thoracic diameter)
More than 2 involved sites
A defined combination of B symptoms and elevated ESR: B symptoms and an ESR over 30 mm/hour; an ESR over 50 mm/hour without B symptoms
Extranodal extension, i.e., any tumor spread involving tissues other than those of the lymph nodes; spleen; thymus; Waldeyer's tonsillar ring appendix; and Peyer's patches
European Organization for the Research and Treatment of Cancer (EORTC)⁹
The mediastinal mass ratio (maximum width of mass/maximum intrathoracic diameter) of >0.35 at T5-T6
Three or more involved sites
Age $\geq$ 50 years at diagnosis
A defined combination of B symptoms and elevated ESR: B symptoms and an ESR over 30 mm/hour or an ESR over 50 mm/hour without B symptoms
National Cancer Institute of Canada (NCIC)/Eastern Cooperative Oncology Group (ECOG)¹⁰
Mediastinal mass ratio >0.33 or a mass >10 cm
More than 3 involved sites
Age $\geq$ 40 years at diagnosis
ESR >50 mm/hour
Mixed cellularity histology
National Comprehensive Cancer Network (NCCN)¹¹
Bulky disease
Extranodal extension
ESR >50 mm/hour
More than 3 involved sites

Table 2. Unfavourable risk factors according to GHSg, EORTC and NCIC groups⁷⁻¹¹

A retrospective analysis was conducted of 1,173 patients diagnosed with early-stage classical Hodgkin lymphoma, comparing the GHSg, EORTC and NCCN models. The results demonstrated that the three models had similar prognosis classifications for patients with early-stage

cHL(Classical HL), with 56%, 55%, and 57% classified as having an unfavourable prognosis, respectively.¹²

Treatment Modalities

Limited stage – Favourable

Radiation therapy (RT) and combined modality therapy (CMT), which includes chemotherapy and RT, result in a cure for most patients with favourable limited-stage HL. However, RT results in high rates of long-term complications, including the risk of secondary cancers and cardiovascular toxicities.¹² To minimize the adverse side effects associated with treatment, recent clinical studies have explored response-based approaches and the use of newer drugs to decrease the strength of conventional chemotherapy and/or RT.⁹

Non-PET adapted approach

The GHSg (German Hodgkin Study Group) HD⁷ trial reported superior progression-free survival (PFS) with CMT compared to extended field RT alone; however, it did not demonstrate any overall survival (OS) benefit. Treatment-related complications, including secondary solid tumors and pulmonary and cardiovascular diseases, accounted for the majority of deaths.¹³ To reduce these complications, subsequent trials explored reducing the dose of RT, as well as the number of cycles of chemotherapy. The GHSg HD10 trial compared 4 groups: 4xABVD (adriamycin, bleomycin, vinblastine, dacarbazine) and 30Gy radiation therapy (RT), 4xABVD and 20 Gy RT, 2xABVD and 30Gy RT and 2xABVD and 20Gy RT. A recent long-term clinical trial follow-up demonstrated that 2xABVD and 20-Gy RT was non-inferior to 4xABVD and the 30-Gy group, reporting a PFS of 87% each and OS of 94% each.¹³ The GHSg HD13 trial demonstrated that omission of bleomycin and/or dacarbazine resulted in a significant reduction in tumor control.¹⁴

PET adapted approach

In the GHSg HD16 clinical trial, patients received 2x ABVD and 20Gy IFRT or PET-guided treatment without IFRT after negative PET-2. The CMT group demonstrated a five-year PFS of 93.4% vs 86.1% in the chemotherapy-only group.¹⁵ Similar results were seen in the United Kingdom RAPID trial¹⁶ and the EORTC H10F trial⁹. In the EORTC H10 trial, Stage I-II HL favourable risk patients were randomized between control arm therapy with ABVD x3 + involved node RT (INRT), with all patients undergoing PET following 2 cycles of ABVD. In the experimental arm (no INRT group), patients received ABVD x2, then a PET scan, followed by ABVD x 2 if it was negative, and BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) escalated x 2 plus INRT if positive. In the PET negative group and experimental arm, the difference in PFS was 11.9%, not meeting the non-inferiority endpoint. There was no difference in OS. For patients with PET-positive

disease, the 5-year PFS was 77% vs 91% ($P=0.002$) and the 5-year OS was 89% vs 96% ($P=0.06$), favouring escalated BEACOPP compared to ABVD + INRT.⁹

Both the UK RAPID and EORTC H10 trials support the use of radiotherapy despite a negative interim PET. Based on these large international trials, the NCCN and ESMO guidelines recommend CMT with 2 x ABVD with 20-Gy RT in limited stage favourable HL. For PET positive patients after 2 x ABVD, the ESMO guidelines recommend 2x escalated BEACOPP plus 30-Gy involved site radiation therapy (ISRT).⁴ However, the difference in PFS was small, and there was no OS advantage. Based on these findings, radiotherapy can be omitted in certain patients based on their therapeutic goals and characteristics, thereby avoiding long-term RT sequelae such as secondary malignancies. Case examples include patients with cardiovascular comorbidities receiving a cardiac RT, or avoidance of mediastinal lymph node region RT in young women.²

Limited stage – Unfavourable

Non-PET adapted approach

The GHSG HD 11 clinical trial concluded that 4 cycles of ABVD should be followed by 30Gy RT; and that moderate dose escalation using BEACOPP (baseline) did not significantly improve outcomes in limited-stage unfavourable disease.⁸ However, the HD14 trial demonstrated intensified therapy with 2 x escalated BEACOPP, and 2 X ABVD (2+2) followed by IFRT significantly improved tumor control. The 2 +2 approach is associated primarily with acute hematologic toxicity; however, no long-term toxicity or effect on OS has been demonstrated to this point.³

PET adapted approach

In the H10U trial, 79.9% of patients demonstrated PET 2 negativity. This suggests that PET after 2 cycles of ABVD might help to individualize treatment in a subset of patients with bulky mediastinal disease, or in those who are PET 2 positive in need of an intensified treatment.⁹ The H10U study indicates that intensified therapy consisting of 2 cycles of ABVD followed by 2 cycles of escalated BEACOPP, along with 30-Gy INRT, is more effective vs the standard 4 cycles of ABVD and 30-Gy INRT in patients who are PET-2 positive. It is important to note that the majority of patients in the H10 group (77.8% who were PET-2 negative) could still be treated effectively with only 4 cycles of ABVD.⁹ A preliminary analysis of the HD 14 trial revealed a decrease in the ovarian reserve; however, no significant differences in female fertility potential after two cycles of escalated BEACOPP and two cycles of ABVD, compared with four cycles of ABVD.¹⁷

The NCCN and ESMO guidelines recommend 4 cycles of multi-agent chemotherapy followed by 30-Gy IFRT or ISRT for patients with limited stage unfavourable

disease. Both 2+2 and 4x ABVD are cited as relevant strategies. A PET-guided strategy similar to that of H10U is recommended by the ESMO guidelines.^{11,18} BEACOPP is used only in patients <60 years of age with no comorbidities, and in younger patients following patient counselling regarding the risks of decreased ovarian reserve.

Elderly Hodgkin lymphoma

Prospective trial data are lacking in this population sub group. Intensive regimens such as BEACOPP are not recommended due to increased treatment-related mortality. Two cycles of ABVD combined with 20-Gy IF/ISRT is a viable and successful treatment option for elderly patients with early-stage favourable Hodgkin lymphoma.¹⁹ Four cycles of ABVD have been linked to a significant rate of severe side effects, particularly hematotoxicity and lung toxicity related to bleomycin, leading to an increased risk of treatment-related mortality compared to only 2 cycles of ABVD.²⁰ In patients with early-stage unfavourable Hodgkin lymphoma, a safer treatment approach is 2 cycles of ABVD followed by 2 cycles of AVD and 30-Gy IF/ISRT. Gunther et al demonstrated that partial omission of bleomycin resulted in a 99% freedom from relapse at 8 years.²¹

Conclusion

The majority of patients with early-stage HL can now be cured with a risk-adapted approach. PET-adapted strategies have been tested to reduce treatment-associated toxicity, which involves reducing RT fields. Long-term survival rates for patients with a favourable risk profile are excellent with ABVD plus 20-Gy ISRT or INRT. Patients in the unfavourable risk group typically receive 4 cycles of multi-agent chemotherapy plus 30-Gy limited-field RT. When optimal tumor control is the primary objective, escalated BEACOPP followed by ABVD (2 +2) is preferred over ABVD. For patients who prioritize the reduction of treatment-associated toxicity, a PET-guided chemotherapy strategy with escalated BEACOPP administered only in PET-positive patients after 2 initial cycles of ABVD is an effective and less toxic alternative to 2+2. Consolidative RT can improve disease control in early-stage HL; however, the omission of RT might be possible in selected patients with PET-negative disease (**Figure 1**). In patients >60 years of age, omission of bleomycin after 2nd ABVD is recommended.

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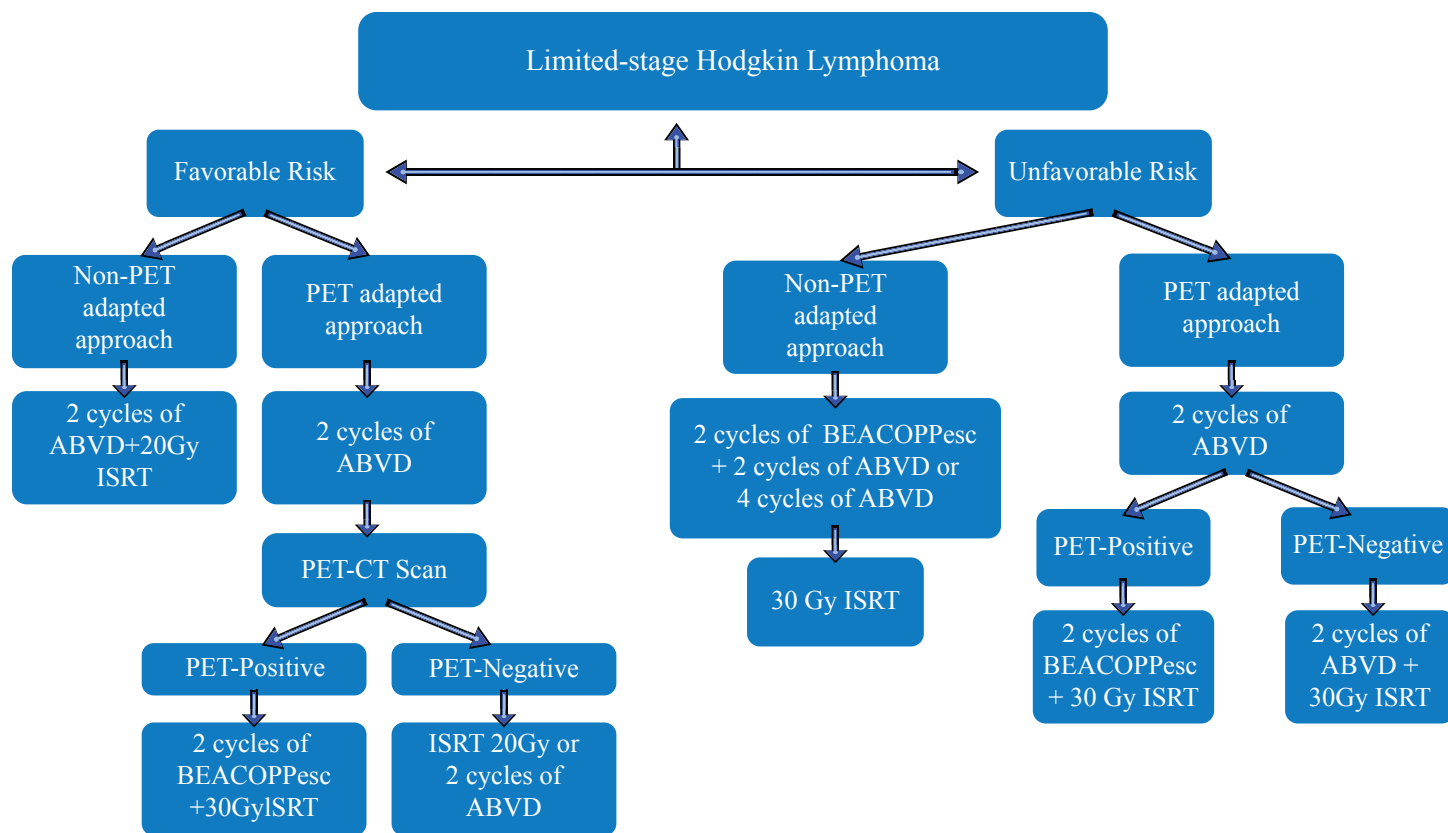


Figure 1. Non-PET approach based on GHSG HD10¹³ and GHSG HD14³ clinical studies, and PET- guided approach based on EORTC/LYSA/FIL/ H10 studies;⁹ Adapted from ESMO guidelines.⁴

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TYROSINE KINASE INHIBITORS FOR THE FRONTLINE MANAGEMENT OF CML: AN OVERVIEW

Introduction

The introduction of Tyrosine Kinase Inhibitors (TKI) for the treatment of chronic myeloid leukemia (CML) has revolutionized CML therapy. These agents have increased the life expectancy of CML patients to 98% of those in the general population¹. Since the first approval of imatinib for CML treatment (by the US FDA in 2001²), three additional TKIs have been approved for the indication of frontline therapy in CML during chronic phase (CP), including: dasatinib³, nilotinib⁴ and bosutinib⁵. This article will discuss the initial steps for newly diagnosed CML patients, its frontline therapy, and its management.

Goal of Frontline CML Treatment

The goal of CML treatment has evolved over last 2 decades in parallel with drug development. When imatinib was approved for CML therapy, the main goal was the reduction of transformation to blastic phase (BP) and the prolongation of survival². As treatment evolved, this goal changed to achieving complete cytogenetic response (CCyR) or major molecular response (MMR) within a certain timeframe³⁻⁵. With successful replication in multiple TKI discontinuation studies for the treatment-free remission (TFR) attempt⁶⁻⁸, the achievement of deep molecular response (DMR), which is required for qualification of TFR attempt, is also considered an ultimate goal of CML therapy⁹. In addition, quality of life (QoL) during CML therapy has been

underscored over last 10 years as another important goal of treatment given that several TKIs can induce significant and critical toxicities.

The determination of frontline CML treatment goal(s) should be individualized for patients given the heterogenous nature of the illness and will require careful consideration of multiple factors including demographic characteristics, medical, and the physical or social condition of the patient as well as the patient's lifestyle. Careful discussion with the patients and their families prior to frontline TKI drug selection is critical.

Disease Risk Assessment

For the initial risk assessment of CML, three risk stratification systems have been frequently utilized⁹:

1) Sokal risk score, 2) Hasford risk score, 3) EUTOS long term survival (ELTS) score⁹. While the Sokal and Hasford risk scores had been traditionally used for initial risk assessment over the last 4 decades, the ELTS score has been shown to predict the probability of long-term antileukemic efficacy of TKI therapy and CML-related death following frontline imatinib therapy¹⁰. The following formula can be used to calculate the ELTS score. Additionally, an online calculator can be found at https://www.leukemia-net.org/leukemias/cml/eutos_score/

ELTS score =

$0.0025 \times (\text{age in completed years}/10)^3$

+ $0.0615 \times \text{spleen size below costal margin}$

+ $0.1052 \times \text{blasts in peripheral blood}$

+ $0.4104 \times (\text{platelet count}/1000)^{-0.5}$

An ELTS score value ≤ 1.5680 defines the low-risk group

An ELTS score value > 1.5680 but ≤ 2.2185 defines the intermediate-risk group

An ELTS score value > 2.2185 defines the high-risk group

The detection of additional chromosomal abnormalities (ACA) is also extremely helpful when identifying high-risk patients⁹. High-risk ACA need to be closely monitored, which include trisomy 8, a second Ph chromosome (+Ph), isochromosome 17[i(17)], +19, -7/7q-, 11q23 or 3q26.2 aberration, and complex aberrant karyotypes⁹.

In the last version of the European LeukemiaNET (ELN) 2020 recommendations for CML, patients with a high-risk ELTS score or high-risk ACA were classified in a “warning” category at baseline due to their higher risk of progression and poorer response to TKI therapy, thus necessitating careful monitoring of the disease during administration of TKI therapy⁹.

Comorbidities and Other Medical Condition Assessments

Based on the ELN recommendation in 2020⁹, the initial diagnostic workup and investigation should include physical examination (especially for spleen size), CBC with differential, bone marrow aspirate and biopsy with chromosome banding analysis for cytogenetics, RT-PCR for BCR-ABL with biochemical profile, and hepatitis B-serology. In our center, lipid profile, HbA1C, urinalysis, ECG, and a chest X-ray are also included as part of the routine investigation for newly diagnosed CML patients.

Recently, it has been increasingly recognized that there is an elevated risk of cardiovascular toxicities associated with the use of 2nd generation TKIs including nilotinib and ponatinib, such as arterial occlusive events¹¹. Accordingly, it can be onerous to assess a CML patient’s cardiovascular risk profile and underlying comorbidities during their clinical visits. The Framingham cardiovascular risk score can be calculated based on age, sex, smoking history, total and HDL cholesterol level, systolic blood pressure, as well as the use of antihypertensive treatment¹².

However, higher risk groups for cardiovascular comorbidities should be referred to a cardiologist for further evaluation, in addition to a 2D echocardiography.

Consideration of Drug-Drug Interactions

Another factor that should be kept in mind during the process of frontline TKI drug selection is the potential for drug-drug interactions. A careful review of the patient’s whole list of medications is required¹³. Drug-drug interactions can result in CML patients suffering from toxicities from the use of TKI itself or from concomitant medications beyond TKI therapy.

Management Prior to Frontline TKI Treatment

Prior to initiation of frontline TKI drug treatment, a short course of hydroxyurea can be administered with allopurinol to prevent tumor lysis syndrome, which can occur with TKI therapy⁹. During this phase, vigorous hydration is also strongly encouraged.

While white blood cell (WBC) and/or platelet counts can be controlled with hydroxyurea, consideration can be given for which TKI drug should be used as frontline TKI therapy in an individual patient. In some provinces, this choice is restricted by reimbursement criteria.

Frontline TKI Drug Selection

Currently, 4 TKI agents are commercially available: imatinib, nilotinib, dasatinib and bosutinib. Their efficacy, toxicity profiles, and long-term toxicity are summarized in **Table 1**.

Three Potential Scenarios for Individualized Frontline TKI Drug Selection

To help clinicians appreciate the approach to individualized TKI drug selection, three scenarios are presented below.

1. 2nd generation TKI in a 55-year-old patient with diabetes; aiming for TFR

A 55-year-old man has a diagnosis of CML-CP with a history of diabetes. With approximately 30+ years of life expectancy, the ultimate treatment goal should be treatment-free remission. The disease risk classification is intermediate, and the cardiovascular risk profile is low. The patient prefers a once-daily agent due to his work environment. Accordingly, the decision was made to proceed with dasatinib frontline therapy to increase the chance of achieving DMR while nilotinib is contraindicated due to diabetes.

2. Imatinib in a 82-year-old patient with multiple cardiopulmonary comorbidities

An 82-year-old lady has a diagnosis of CML. She has multiple comorbidities of coronary artery disease, chronic obstructive pulmonary disease, inflammatory bowel disease with diabetes. A practical treatment goal is disease

	Imatinib	Dasatinib	Nilotinib	Bosutinib
Class	1 st generation-TKI	2 nd generation-TKI	2 nd generation -TKI	2 nd generation-TKI
Dose	400 mg once daily, with meal	100 mg once daily	300 mg twice daily dosing with dietary restriction	400 mg once daily
Key data for efficacy	higher CCyR and MMR & better PFS and OS than Interferon/AraC therapy	Higher MMR and MR4 than imatinib; Similar PFS/OS to imatinib	Higher MMR and MR4 than imatinib; Similar OS to imatinib	Higher MMR than imatinib
MMR	60-80% at 5 yrs	76% by 5 yrs	77% at 5 yrs	73.9% at 5 yrs
MR4	35-68% at 5 yrs	42% by 5 yrs	66% at 5 yrs	58% at 5 yrs
TFR data	50-60%	50-60%	50-60%	Not reported but expected to be similar
Toxicity profile	Fluid retention, GI symptoms, muscle cramps, fatigue	Pleural effusion (in up to 37% of patients), pulmonary hypertension	Pancreatitis, QTc prolongation, metabolic side effects	Transient diarrhea (in up to 30% of patients); elevation of transaminase
Long-term toxicity	No life-threatening toxicity, but rarely low GFR	Rare cases of pulmonary hypertension and nephropathy	Cardiovascular toxicity of arterial occlusive event	Not known
Reference	IRIS study ²	DASISION study ³	ENESTnd study ⁴	BFORE study ^{5,14}

Table 1. Summary of efficacy and toxicity profile with front line TKI therapy⁹

control to prevent progression and to improve survival. The patient's disease risk is classified as intermediate, but the cardiovascular risk profile is very high. In this case, the decision was made to proceed with imatinib therapy as upfront treatment. Nilotinib, dasatinib and bosutinib were contraindicated due to the patient's underlying comorbidities.

3. 2nd generation TKI in a 33-year-old patient with high risk CML

A 33-year-old patient has a diagnosis of CML-CP with a 20 cm sized spleen palpable on examination. The Sokal and ELTS risk score is classified as 'high'. Chromosome band analysis shows +8 in addition to t(9;22). The patient's disease risk is high, and the cardiovascular risk profile is low. The decision was made to go ahead with nilotinib front line therapy.

Side Effect and Toxicity Management

In most cases, supportive management of side effects and toxicities with the use of TKIs is required. For example, imatinib- and dasatinib-related supportive management includes the use of diuretics for fluid retention, calcium/electrolyte replacement for muscle cramps, and diuretics/short term steroid therapy for pleural effusions⁹.

However, temporary therapy interruption is the first step in managing dasatinib-associated pleural effusion or TKI-induced pancreatic enzyme elevation. Complete cessation of therapy is warranted in cases involving pulmonary hypertension with dasatinib, cardiovascular events, including arterial occlusive disease, with nilotinib, irreversible liver enzyme elevation with bosutinib¹⁵ and gastric antral vascular ectasia with imatinib¹⁶.

Cross disciplinary recommendations from cardiology and endocrinology include the management of cardiovascular and metabolic risk and potential toxicities, by adopting risk assessment and life style modification such as blood pressure/cholesterol/diet/weight management, diabetes prevention, exercise, and smoking cessation¹¹.

Response Monitoring

Following the initiation of front line TKI therapy, molecular response should be monitored on a regular basis (every 3 months) using the *BCR::ABL1* qPCR test⁹. Many of the treatment guidelines suggest determining early molecular milestones based on the *BCR::ABL1* qPCR test results at 3, 6 and 12 months (**Table 2**). If the patient achieves molecular response below 10%^{IS} at 3 months, 1%^{IS} (i.e. MR2) at 6 months, and 0.1%^{IS} (i.e. major molecular response [MMR]) at 12 months, they are classified as having achieved optimal response which precludes the need for treatment switches to other TKIs. If the patient fails to achieve 10%^{IS} at 6 months, 1%^{IS} at 12 months, loses 1% of response at any time after 12 months, develops *ABL1* kinase domain mutations or if any

additional chromosomal abnormalities arise, the patient will be classified as "failure", implying that switching to a new TKI may provide better long-term outcomes. For cases that fall between the optimal response and failure, the patient is classified as "warning", which implies that very careful monitoring of response is required, otherwise there is risk of failure.

In cases of treatment failure, activation of the *ABL1* kinase domain mutation (KDM) test is the first step in the ongoing monitoring of response^{9,17}. Clinicians should note that the analytical sensitivity detection limit with Sanger sequencing-based KDM tests is about 10-20%, meaning that the KDM test fails to capture some *ABL1* KDMs due to this detection limit, particularly in patients with PCR levels below 1%¹⁸.

Once a patient achieves 1-0.1%^{IS} or a deeper response, besides *BCR::ABL1* qPCR, it is recommended to repeat the chromosome banding analysis test from the marrow sample. About 10% of CML patients achieve responses that could develop a clonal evolution in Philadelphia chromosome negative clone¹⁸. Some of those cases, particularly with monosomy 5/7 or del(5) or del(7), can develop MDS/AML, although its occurrence is rare.

Ongoing and Upcoming Clinical Trials for Frontline Therapy in CML

A novel agent, asciminib, is a first-in-class Specifically Targeting the *ABL1* Myristoyl Pocket (STAMP) inhibitor¹⁹, and is currently being investigated in newly diagnosed CML patients in CP. Results from these pivotal trials are expected to be available in next 1-2 years.

Conclusion

Individualized determination of frontline TKI drug selection is required after careful discussion with newly diagnosed CML patients. This determination process includes detailed discussion involving the goals of CML therapy, disease risk, as well as better understanding underlying comorbidities and concurrent medical conditions before making a final selection of the preferred frontline TKI agent.

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	Optimal*	Warning	Failure
Baseline	-	High risk ACA, high risk ELTS score	-
3 months	$\leq 10\%^{IS}$	$> 10\%^{IS}$	$> 10\%^{IS}$ if confirmed
6 months	$\leq 1\%^{IS}$	$> 1-10\%^{IS}$	$> 10\%^{IS}$
12 months	$\leq 0.1\%^{IS}$	$> 0.1-1\%^{IS}$	$> 1\%^{IS}$
Any time	$\leq 0.1\%^{IS}$	$> 0.1-1\%^{IS}$ Loss of $\leq 0.1\%^{IS}$	$> 1\%^{IS}$ Resistance mutation, high risk ACA
*For patients aiming for TFR, the optimal response (at any time) is $BCR::ABL1 \leq 0.01\%^{IS}$ (i.e. MR4)			

Table 2. Molecular milestone for front line CML therapy based on the $BCR::ABL1$ transcript levels⁹

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VENETOCLAX-BASED LOWER-INTENSITY REGIMENS FOR ACUTE MYELOID LEUKEMIA: CLINICAL PEARLS FOR A NEW STANDARD OF CARE

Introduction

Acute myeloid leukemia (AML) is a heterogeneous disease with variable genetic features and clinical outcomes. The main curative option for AML remains intensive chemotherapy and allogeneic hematopoietic stem cell transplant (HSCT) in selected patients.¹ However, with a median age at diagnosis of 67 years old and frequent comorbidities, a large proportion of patients diagnosed with AML are not eligible for intensive chemotherapy. Until recently, the only treatments available for patients with AML ineligible for intensive chemotherapy were single-agent hypomethylating agents (HMAs) such as azacitidine and decitabine, or low-dose cytarabine (LDAC).²⁻⁴ In older patients with AML, these treatments have been reported to improve outcomes over best supportive care (BSC) alone. However, in clinical studies the expected median overall survival (OS) remained less than 12 months. Fortunately, our increasing knowledge of AML biology has accelerated the development of novel targeted drugs for AML.⁵ Among these, the anti-apoptotic protein B-cell lymphoma 2 (BCL2) inhibitor venetoclax has completely changed the therapeutic landscape of AML, especially for patients who are ineligible for intensive chemotherapy. Venetoclax is approved by Health Canada for use in combination with azacitidine or LDAC for the treatment of newly diagnosed untreated AML in patients who are 75 years or older or have comorbidities precluding the use of intensive

chemotherapy. This approval is based on the two pivotal randomized, Phase 3 trials VIALE-A (azacitidine plus venetoclax) and VIALE-C (cytarabine plus venetoclax).^{6,7} Although seemingly easier to administer than intensive chemotherapy, venetoclax-based regimens are not as “non-intensive” as they are sometimes considered to be. They require the implementation of specific precautionary measures and monitoring to avoid excessive toxicity and optimize patients' outcomes (**Table 1**). We will review here practical points to safely administer venetoclax-based regimens to patients with AML who are ineligible for intensive chemotherapy.

Selection of Appropriate Patients

Defining eligibility for intensive chemotherapy can be challenging. We traditionally use patient-related factors associated with a high risk of severe complications or death during induction to define patients who are ineligible for intensive chemotherapy. The eligibility criteria used in the VIALE-A trial were age ≥ 75 years; symptomatic congestive heart failure (CHF) or left ventricular ejection fraction (LVEF) $\leq 50\%$; chronic stable angina; forced expiratory volume in 1 second (FEV1) or carbon monoxide lung diffusing capacity (DLco) $\leq 65\%$; and Eastern Cooperative Oncology Group (ECOG) performance status of 2 or 3.⁶ These criteria are used for funding of venetoclax in combination with azacitidine for newly diagnosed AML in patients ineligible for intensive chemotherapy.

In addition to patient-related factors, disease-related factors may weigh in the decision to select venetoclax-based lower-intensity regimens. Patients with adverse risk genetics (e.g., complex karyotype, monosomy 5 or 7, TP53 mutation) have poor response to intensive chemotherapy with complete remission (CR) rates of 30%-50%.⁸ Other factors such as an antecedent of hematological neoplasm such as myelodysplastic syndromes (MDS) or myeloproliferative neoplasms (MPN) and previous exposure to chemotherapy or radiotherapy (therapy-related AML) are also associated with lower rates of CR.⁹ In the presence of these adverse risk features, venetoclax-based lower-intensity regimens might be as effective as intensive chemotherapy to achieve CR, but with less toxicity. Therefore, lower-intensity regimens might be more suitable therapeutic options in somewhat older patients (60-75 years) or in those with non-severe comorbidities in whom the tolerance to intensive chemotherapy is uncertain, but the odds of achieving CR with intensive chemotherapy are low. Conversely, older patients or patients with comorbidities diagnosed with chemosensitive AML subtypes such as AML with inv(16)/t(16;16) or t(8;21) or with extramedullary disease, intensive chemotherapy with dose-adjustments as needed is likely the optimal treatment option.

An important exclusion criterion to highlight from the VIALE-A trial is the previous receipt of HMA or chemotherapy for prior history of MDS. These patients were, however, eligible to participate in the VIALE-C trial evaluating LDAC plus venetoclax. Unfortunately, patients with AML progressing from MDS following treatment with HMA or chemotherapy face a poor prognosis with a lack of approved, funded and effective therapies.¹⁰ Despite limited data in this subgroup of patients, the off-label addition of venetoclax to HMA or its use in combination with LDAC may help achieve remission and provide long-term benefit, especially in patients who can subsequently proceed to HSCT in remission.¹¹

Additional factors, such as the patient's preference and care objectives, distance from a leukemia referral centre to undergo induction chemotherapy, and subsequent potential eligibility for HSCT, are important to consider in the selection of frontline therapy for patients with AML.

Prevention of Tumour Lysis Syndrome

Venetoclax can cause tumor lysis syndrome (TLS) by rapidly inducing apoptosis of leukemia cells. The reported risk of TLS with venetoclax-based regimens in AML is approximately 1% to 5%; fortunately, clinically significant TLS with severe renal failure is rare.^{6,7} Risk factors for TLS include baseline chronic kidney disease (CKD); ongoing acute kidney injury (AKI); hyperleukocytosis (white blood cell count [WBC] $>50 \times 10^9/L$); and AML with *NPM1* and/or *IDH1/2* mutations which are more sensitive to venetoclax. It is important to note that the low reported

rates of TLS in clinical trials have been observed with the implementation of preventive measures for TLS which are described here (**Table 1**).

First, because TLS is associated with leukocytosis, the WBC count should be below $25 \times 10^9/L$ prior to initiating venetoclax-based regimens. Reduction of the WBC count can be achieved by hydroxyurea or by intermediate doses of cytarabine (500-1000 mg IV). Second, hydration is extremely important to prevent clinically significant TLS. In admitted patients, IV hydration with normal saline at 100 mL/h is a good strategy, but oral hydration of at least 2,000 mL per day is adequate in compliant patients. It is also important to address and control any baseline AKI prior to initiating venetoclax-based regimens and to avoid the administration of nephrotoxic medications. Third, all patients should be prescribed allopurinol prior to initial administration, and selected patients with spontaneous TLS or at high risk should be administered rasburicase. When prescribing rasburicase, typically I administer a single dose of 3 mg IV which can be repeated as needed depending on uric acid levels and the patient's condition. Last, venetoclax should be initiated at a low dose and escalated to the target dose over a few days to minimize the risk of TLS. In combination with azacitidine, recommended doses of venetoclax are 100 mg on Day 1; 200 mg on Day 2; and 400 mg on Day 3; and onwards (**Figure 1**). In combination with LDAC, a fourth day of ramp-up is added to achieve the target dose of 600 mg on Day 4. To monitor for TLS, it is recommended to perform blood work daily prior to each dose during the ramp-up period and 6 to 8 hours following the initial dose and each increased dose. In the VIALE-A and VIALE-C clinical trials, patients were required to be admitted for the venetoclax dose ramp-up to apply preventive measures and monitor closely for TLS. With the low occurrence of TLS in AML, it is reasonable to consider outpatient ramp-up for low-risk patients as long as the aforementioned preventive measures and monitoring for TLS can be implemented, and patients are compliant to oral hydration.¹²

Prevention of Infectious Complications

Infections remain one of the leading causes of mortality in patients with AML. In the VIALE-A trial, infections of any grade were more frequent with the combination of venetoclax plus azacitidine (84% vs 67%), as was the incidence of neutropenic fever (42% vs 19%). Conversely, the incidence of neutropenic fever was similar between patients treated with LDAC plus venetoclax or placebo in the VIALE-C trial (32% vs 29%). To reduce the risk of febrile neutropenia and infections in patients with AML, prophylactic antimicrobials with a fluoroquinolone for the prevention of bacterial infections, and acyclovir or valacyclovir for the prevention of herpes simplex virus (HSV) or varicella-zoster virus (VZV) infections, are recommended (**Table 1**).¹³

Prevention of tumour lysis syndrome

- Inpatient initiation in high-risk patients
- WBC $\leq 25 \times 10^9/L$ prior to initiating regimen
- IV hydration (NS 100 mL/h) or oral hydration (2,000 mL PO/day)
- Hypouricemic agents: Allopurinol for all and rasburicase in high-risk patients
- Venetoclax dose ramp-up (**Figure 1**)
- TLS blood work monitoring prior to and 6-8 hours following each new dose

Prevention of infectious complications

- Anti-bacterial prophylaxis (e.g., levofloxacin 500 mg PO daily)
- Anti-viral prophylaxis (e.g., valacyclovir 500 mg PO BID)
- Anti-fungal prophylaxis (e.g., posaconazole 300 mg PO daily)
- HBV re-activation prophylaxis as needed (e.g., entecavir 0.5 mg PO daily)
- Consider stopping anti-bacterial and anti-fungal prophylaxis when ANC $\geq 1.0 \times 10^9/L$

Response assessment and management of cytopenia

- BMA assessment at the end of cycle 1 (between Days 21 and 28) and at the end of every cycle until achievement of CR/Cri (complete remission with incomplete hematological recovery)
- Proceed with next cycle at day 29 if persistent disease
- Proceed with next cycle when ANC $\geq 1.0 \times 10^9/L$ and platelet count is $\geq 100 \times 10^9/L$
- Venetoclax duration reduction (21, 14 or 7 days) if persistent cytopenia ≥ 42 days
- Avoid delaying next cycle for more than 4 weeks
- Use G-CSF in patients with CR/Cri and mild/moderate neutropenia (ANC $> 0.5 \times 10^9/L$)

Venetoclax dose adjustments

- Dose reduction of 50% with moderate CYP3A4 inhibitors (e.g., fluconazole, isavuconazole, ciprofloxacin, diltiazem, etc.) – Target dose 200 mg with azacitidine
- Dose reduction of 75% with strong CYP3A4 inhibitors (e.g., posaconazole, voriconazole, ritonavir etc.) – Target dose 100 mg with azacitidine
- Avoid CYP3A4 inducers and use alternative medications

Table 1. Clinical pearls with venetoclax-based lower-intensity regimens; courtesy of Guillaume Richard-Carpentier, MD

Venetoclax dose ramp-up	Day 1	Day 2	Day 3+
No CYP3A4 inhibitor	 100 mg	 200 mg	 400 mg
Moderate CYP3A4 inhibitor (Fluconazole, Isavuconazole, Ciprofloxacin, Diltiazem)	 50 mg	 100 mg	 200 mg
Strong CYP3A4 inhibitor	 20 mg	 50 mg	 100 mg

Figure 1. Venetoclax initiation dose ramp-up with appropriate dose adjustments for concomitant administration of medications with CYP3A4 inhibition.

There are no randomized clinical trials evaluating the benefit of prophylactic antimicrobials in patients with AML receiving non-intensive regimens, however, the depth and duration of neutropenia (generally $<0.5 \times 10^9/L$ for >7 days) observed with venetoclax-based regimens justifies their use. For bacterial prophylaxis, I prefer levofloxacin because of its daily administration and absence of CYP3A4 inhibition in contrast to ciprofloxacin. Unfortunately, invasive fungal infections are frequent in patients treated with venetoclax-based regimens, with one clinical study reporting a rate of 12.6%.¹⁴ Therefore, antifungal prophylaxis with a triazole with anti-mold activity (posaconazole, voriconazole or isavuconazole) is also recommended.^{13,15} Unfortunately, because of the elevated cost and restrictive funding criteria for these drugs, anti-mold triazoles for prophylaxis of aspergillosis in patients with AML are not accessible in all jurisdictions. At the least, fluconazole may prevent oropharyngeal or esophageal candidiasis and candidemia in these patients. Importantly, azole antifungals are CYP3A4 inhibitors and dose adjustments for venetoclax are required when these drugs are administered concomitantly as described below (**Figure 1**). Patients at risk of hepatitis B virus (HBV) reactivation (anti-HBc positive) should also receive a nucleoside reverse transcription inhibitor (e.g., entecavir or tenofovir). Prophylaxis for *Pneumocystis jirovecii* is not routinely recommended but might be considered in patients with additional risk factors.

In summary, I prescribe triple prophylaxis with levofloxacin, posaconazole and valacyclovir in patients treated with venetoclax-based lower-intensity regimens which I continue until they achieve remission (**Table 1**). Once in remission with neutrophils $\geq 1.0 \times 10^9/L$, I typically continue valacyclovir and hold anti-bacterial and anti-fungal prophylaxis as long as episodes of neutropenia, if any, are brief (<7 days) and non-severe.

Monitoring of Response and Management of Cytopenia

The addition of venetoclax to LDAC or azacitidine is associated with higher rates of severe and prolonged cytopenia. During the first cycle, I monitor complete blood counts (CBC) twice weekly as the majority of patients require transfusions. At the end of cycle one of azacitidine plus venetoclax, most patients will have absolute neutrophils count (ANC) $<0.5 \times 10^9/L$ and platelets $<50 \times 10^9/L$. Therefore, it is critical to perform a bone marrow aspiration (BMA) and biopsy at the end of the first cycle to evaluate if the cytopenia is related to persistent disease or to the effect of treatment. Approximately 50% of patients who achieve remission with venetoclax-based regimens will do so after the first cycle and others generally after the second cycle. Typically, I perform the end of cycle one BMA around Day 21 in order to know by Day 28 if patients have achieved morphological remission ($\leq 5\%$ bone marrow blasts.) In patients with persistent disease, it is

recommended to proceed with a second cycle without waiting for count recovery. In patients with remission, but without complete count recovery (ANC $<1.0 \times 10^9/L$ and/or platelets $<100 \times 10^9/L$), it is recommended to wait for count recovery prior to proceeding with cycle two. In these situations, I stop the venetoclax whenever I obtain the BMA results even if the patient has not completed 28 days of treatment. When ANC recovers i.e., $\geq 1.0 \times 10^9/L$ and the platelet count is $\geq 100 \times 10^9/L$ within two weeks following the end of the cycle (Day 42), patients can proceed with the next cycle without dose adjustments. In patients with some degree of count recovery with ANC $\geq 0.5 \times 10^9/L$ and a platelet count of $\geq 50 \times 10^9/L$, I typically proceed with the next cycle, with adjustment of the duration of venetoclax to 21 days or 14 days, depending on the duration of the previous cycle. In patients with no count recovery beyond 42 days, I repeat a BMA to reassess if the leukemia is not in remission or if bone marrow aplasia is persistent. In patients with persistent aplasia without count recovery, I proceed with a next cycle of treatment after delaying a maximum of 3 to 4 weeks. In these circumstances, I adjust treatment by decreasing the duration of venetoclax to 7 or 14 days and sometimes azacitidine to 5 days instead of 7 days. In patients with persistent cytopenia, relapse is almost guaranteed without treatment for a prolonged period. On subsequent cycles, I apply the same algorithm, proceeding to the next cycle whenever ANC recovers $\geq 1.0 \times 10^9/L$ with a platelet count of $\geq 100 \times 10^9/L$ (or at least ANC $\geq 0.5 \times 10^9/L$ and platelets $\geq 50 \times 10^9/L$) without dose adjustments if cycle lengths are less than 42 days. Additionally, I decrease the duration of venetoclax if cytopenia persists beyond 42 days. Despite the fact that the VIALE-A and VIALE-C clinical trials had planned protocols for continuous administration of venetoclax, the majority of patients will generally receive venetoclax for 14 to 21 days on steady-state and have a cycle duration of approximately 5 weeks. Post-hoc data from these trials have shown that patients with these adjustments have similar outcomes vs those who can proceed with treatment without modifications and delays. Filgrastim (G-CSF) can be administered without any concerns in patients with mild-to-moderate neutropenia after achieving complete remission. I use it in patients who have been able to spontaneously recover neutrophils in previous cycles and who are on a stable duration of venetoclax and cycle length. Depending on patients' blood counts and the risk of relapse based on genetic features, I repeat BMA every 3 to 6 cycles or whenever there are new, significant cytopenias suggestive of relapse. If patients relapse after an initial response, I sometimes re-increase the duration of venetoclax to 28 days and azacitidine to 7 days in an attempt to salvage their response or at least stabilize their disease while considering alternative therapies, if any are available.

Venetoclax dose adjustments

Venetoclax is metabolized by CYP3A4 and concomitant administration of CYP3A4 inhibitors or inducers will affect the plasma concentration of venetoclax. Therefore, dose adjustments are warranted in patients receiving pharmaceuticals that alter CYP3A4 metabolism in order to avoid excessive toxicity, especially severe and prolonged myelosuppression (**Table 1**). Strong CYP3A4 inhibitors such as posaconazole, voriconazole and ritonavir require venetoclax dose reduction of 75% to 90%.¹⁶ Therefore, patients treated with venetoclax in combination with azacitidine should start the ramp-up with venetoclax 20 mg on Day 1; 50 mg on Day 2; and 100 mg on Day 3 and onwards, with some data even suggesting a steady dose of 70 mg of venetoclax with concomitant administration of strong CYP3A4 inhibitors, especially posaconazole (**Figure 1**). With moderate CYP3A4 inhibitors such as ciprofloxacin, fluconazole and diltiazem, the venetoclax dose should be adjusted to 50% of the target dose. Therefore, in combination with azacitidine, venetoclax should be administered at a dosage of 50 mg on Day 1; 100 mg on Day 2; and 200 mg on Day 3 and onwards with a moderate CYP3A4 inhibitor (**Figure 1**). As mentioned above, I prefer levofloxacin for anti-bacterial prophylaxis because the additive effect of ciprofloxacin with a triazole anti-fungal on CYP3A4 inhibition is unknown and informed recommendations for venetoclax dose-adjustments cannot be made. Grapefruit, starfruit and Seville oranges also contain a CYP3A4 inhibitor and should be avoided by patients taking venetoclax. CYP3A4 inducers such as carbamazepine, phenytoin or rifampin should be avoided as they may decrease the clinical effect of venetoclax. Alternative drugs should be utilized instead.

Conclusion and Future Perspectives

The addition of venetoclax to lower-intensity regimens has significantly changed the therapeutic landscape for patients with newly diagnosed AML who are ineligible for intensive chemotherapy. These regimens improve remission rates and overall survival over single-agent LDAC or HMAs, but require specific monitoring measures to minimize the risk of complications and optimize patients' outcomes (**Table 1**). Specific measures include hydration, hypouricemic agents, prior cytoreduction, and venetoclax dose ramp-up to decrease the risk of TLS; infectious prophylaxis to prevent neutropenic fever episodes and infections; and venetoclax dose-adjustments to manage drug interactions. The time to response (TTR) is also more rapid with venetoclax-based lower-intensity regimens vs single-agent LDAC or HMA. Performing a bone marrow assessment following the first cycle and periodically thereafter is critical to determine if the cytopenia is related to relapsed or refractory leukemia, or to treatment effect, and to subsequently manage the cytopenia appropriately. Despite providing better outcomes for patients who are ineligible for intensive chemotherapy, approximately

one-third of patients will not achieve remission with these regimens and the majority of patients achieving remission will nonetheless eventually relapse. Thankfully, the future holds promise for patients with triplet combination regimens including FLT3, IDH1/2 inhibitors or monoclonal antibodies being evaluated to further improve efficacy and outcomes in this patient population.

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