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Approach to Patients with Acute Myeloid Leukemia in First Relapse: A Practical Guide for Canadian Hematologists

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Introduction

Acute myeloid leukemia (AML) is an aggressive and heterogeneous type of blood cancer associated with significant morbidity and mortality. Despite major improvements in the treatment of AML over the last decade, many patients unfortunately present with relapsed or refractory (R/R) disease after first-line standard treatment.[1]

With traditional high-intensity induction chemotherapy (IC) for AML, such as

the 7+3 regimen, complete remission (CR) rates are about 75–80%, and in those who achieve remission, the relapse rate is approximately 40–50%.[2] With less intensive regimens, such as azacitidine plus venetoclax (Aza-Ven), composite CR rates are about 65–70%, and in those who respond, about half will relapse within 2 years.[3] Relapses mainly result from the survival of leukemia stem cells (LSCs), which may acquire additional mutations under the selective pressure of therapy and expand to drive disease recurrence.[4] The majority of patients with R/R AML present with adverse-risk genetic features, which are associated with a lower median overall survival (OS) of less than 6 months. With second-line therapy for R/R AML, the overall response rates (ORRs) ranged between 20%–45%,[5] underscoring the unmet need regarding the best therapeutic approach for these patients.

This review aims to help the reader quickly identify the most common current standard salvage chemotherapy regimens and targeted agents used in the first relapse setting of AML and discuss the ongoing challenges in treating this patient population.

Genetic Landscape Upon Relapse

As shown by Nuno *et al*., relapse in AML is often not driven by new genetic mutations but by epigenetic evolution, in which leukemia cells alter gene regulation and chromatin states to become more resistant to therapy, with different clones converging toward similar resistant phenotypes.[6] It unfortunately still remains poorly understood how these epigenetic changes drive chemo-resistance and how this could be overcome to achieve remission.[7] Despite the relative stability of genetic features in R/R AML, certain gene mutations (*FLT3*, *IDH1/2, NPM1*) and cytogenetic abnormalities (*KMT2A* rearrangement) warrant retesting at relapse, since targeted agents may be used in patients harbouring these genetic abnormalities. For example, approximately 10% of patients with AML will present with changes in their *FLT3* mutational status at the time of R/R disease and should therefore be retested so that *FLT3* inhibitors, such as gilteritinib, may be considered for treatment.

General Approach and Goals of Care

Selecting optimal salvage therapy in relapsed AML requires a balanced, patient-centred approach. Disease biology should be reassessed, as repeat genetic profiling at relapse may identify new actionable targets. Patient-related factors—including performance status, comorbidities (especially active infections), and goals of care—must also be carefully considered. Finally, transplant eligibility is critical, as allogeneic hematopoietic stem cell transplant (HSCT) remains key to achieving durable remission and potential cure after relapse.

Because R/R AML remains a clinically unmet need, clinical trials evaluating novel drugs or combination therapy should always be considered if available, especially in biologically high-risk disease (e.g., *TP53*-mutated) or after venetoclax failure, where conventional approaches have limited efficacy.[8]

Many patients with R/R AML are not fit for curative treatment. Even low-intensity therapies can cause significant toxicity and impair quality of life. In these cases, a palliative approach with cytoreduction (e.g., hydroxyurea or low-dose cytarabine) and transfusion support may best optimize quality of life and time at home.

Available Salvage Regimens for R/R AML

FLAG-IDA

FLAG-IDA (fludarabine, cytarabine, granulocyte colony-stimulating factor [G-CSF], and idarubicin) is a commonly used regimen for patients with R/R AML deemed fit for IC (**Table 1**). It was evaluated by Pastore *et al*. in 46 patients with R/R AML. This study demonstrated a CR rate of 52%, with similar efficacy in both relapsed and refractory settings.[9] Median OS was 11 months, and disease-free survival was 12 months, with better outcomes observed in patients who had a lower blast burden and favourable cytogenetics. Treatment was associated with acceptable toxicity, including a low induction mortality of 6.6%, although infectious complications and mucositis were common. Importantly, a substantial proportion (46%) of responders was able to proceed to stem cell transplantation, supporting FLAG-IDA as an effective salvage regimen and a bridge to transplant in R/R AML.

FLAG-IDA plus Venetoclax

DiNardo et al., conducted a phase IIB study of 61 patients with R/R AML treated with FLAG-IDA plus venetoclax, demonstrating high efficacy (**Table 1**).[10] In the R/R cohort, the regimen achieved a composite CR rate of 64%, with minimal residual

disease (MRD)-negativity in 74% of responders. Survival outcomes were favourable, with a 3-year OS of 32%, particularly among patients in first salvage with *TP53* wild-type disease (3-year OS of 51%). Notably, 57% of R/R patients proceeded to HSCT, supporting its role as an effective salvage bridge-to-transplant strategy with an acceptable safety profile. Molecular subgroups known to be sensitive to venetoclax-based therapy, including *NPM1, IDH1*, and *IDH2*, demonstrated excellent outcomes, with a composite CR rate of 100% and a 12-month OS of 83% in the R/R AML setting. In contrast, mutations in tumour suppressor genes, such as *TP53, WT1, FBXW7*, and *PHF6*, which are more common in non-responders and associated with treatment resistance, were linked to significantly lower composite CR rates (38% vs. 77%; P=0.021), demonstrating the ongoing challenge of treating these subgroups of patients.

Based on this phase II trial,[10] and retrospective studies,[11] adding venetoclax to FLAG-IDA for R/R AML appears to be associated with higher rates of deep remission than IC alone. However, no randomized trial has yet addressed this question, and the availability of venetoclax in this setting can be a challenge. Addition of venetoclax could be considered particularly in patients with *NPM1*- or *IDH1/2*-mutated disease or *TP53* wild-type status, and in the first salvage setting in patients aiming for a curative intent who are likely eligible for HSCT. Previous exposure to venetoclax and the availability of more appropriate biology-directed treatment options should also be considered.

MEC

The MEC regimen (mitoxantrone, etoposide, and cytarabine) is also commonly used for R/R AML (**Table 1**). The phase II study by Amadori et al. evaluated MEC in 32 patients with high-risk R/R AML, including primary refractory disease, early relapse, and post-transplant relapse.[12] The regimen produced a high CR rate of 66%, with better responses in younger patients and those in early relapse, while patients with primary refractory disease had lower response rates. Despite this activity, remissions were short (median 16 weeks), and OS was limited (median 36 weeks). Treatment was associated with universal severe myelosuppression and a high rate of infectious complications (91%), but early mortality was relatively low at 6%, and non-hematologic toxicity was generally manageable. Overall, MEC demonstrated significant anti-leukemic activity with acceptable toxicity in a poor-risk population, supporting its role as a salvage regimen, although without evidence of durable long-term benefit.

Among IC regimens, there is no universally superior regimen for patients with R/R AML. MEC and FLAG-IDA appear broadly comparable based on retrospective data,[13] but this has not yet been confirmed in a head-to-head randomized trial. Although larger studies have been performed with FLAG-IDA plus venetoclax, MEC has also been reported as a backbone to add venetoclax in the R/R setting.

Hypomethylating Agents (HMAs) Plus Venetoclax

HMAs, such as azacitidine, in combination with venetoclax, have become the standard of care for patients with newly diagnosed AML who are ineligible for IC, based on the VIALE-A trial (**Table 1**).[3] In R/R settings, HMAs (azacitidine or decitabine) plus venetoclax are also increasingly used, with several retrospective studies describing the use of this combination. As shown by Aldoss *et al.*,[14] in a retrospective cohort of 90 patients with R/R AML treated with venetoclax plus HMA, the composite CR rate was 46%, with many responses occurring early and frequently achieving MRD-negativity. Patients who achieved CR/complete remission with incomplete count recovery (CRi) had significantly improved OS compared to non-responders (median OS 16.6 vs. 5.1 months), while the median OS for the overall cohort was 7.8 months, highlighting the clinical benefit of response to venetoclax-based therapy in this high-risk population.

Additionally, as shown by Unglaub and colleagues, venetoclax plus azacitidine is an effective and less toxic salvage strategy in relapsed AML, achieving higher response rates than standard IC and enabling successful bridging to HSCT in approximately 70% of patients.[15] However, no prospective clinical trials have yet confirmed the added benefit of venetoclax in this challenging-to-treat population.

Beyond fitness, the choice between IC and HMA plus venetoclax in R/R AML may be guided by disease biology, aggressiveness of the relapse, prior exposure to venetoclax, and transplant intent. When rapid cytoreduction is required in a fit patient in first salvage with a clear plan to proceed to HSCT, IC with or without venetoclax is likely a preferred approach. Conversely, Aza–Ven may

Chemotherapy Regimen	Dosage and Schedule	ORR (*%, n*)	mOS rate (*months*)	Reference
FLAG-IDA	• Fludarabine 30 mg/m^2 IV over 30 min, D 1–5 • Cytarabine, 2000 mg/m^2 IV over 4 h, D 1–5[A] • Idarubicin 10 mg/m^2 IV, D 1–3 • G-CSF (Filgrastim) 5 mcg/kg SC D 6-until ANC recovery	52 (24/46)	11 (1–25)	[12]
FLAG-IDA plus Venetoclax	• Fludarabine 30 mg/m^2 IV , D 2–6 • Cytarabine,1500 mg/m^2 IV, D 2–6 • Idarubicin, 6 mg/m^2 IV, D4–5[B] • G-CSF (Filgrastim) 5 mcg/kg SC, D1–7 • Venetoclax 400 mg PO daily, D 1–7[C]	67 (41/61)	12 (9–34)	[13]
MEC	• Mitoxantrone 6 mg/m^2 IV, D 1–6[D] • Etoposide 80 mg/m^2 IV, D 1–6 • Intermediate-dose Cytarabine 1000 mg/m^2 IV D 1–6	66 (21/32)[E]	4 (0.5–29.5)[F]	[14]
Azacitidine plus Venetoclax	• Azacitidine,75mg/m^2 SC daily for 7 days • Venetoclax PO 100mg D1, 200mg D2, 400mg D3–28[F]	46 (41/90)	7.8 (5.9–15.5)	[3,15]
Gilteritinib	• Gilteritinib 120 mg PO, D 1–28[G]	68, (167/247)	9.3 (7.7–10.7)	[17]
Ivosidenib	• Ivosidenib 500 mg PO, D 1–28	42, (52/125)	8.8 (6.7–10.2)	[18]

Table 1. Salvage Therapies for Relapsed/Refractory AML; *courtesy of Cristiano Machado de Freitas, MD and Guillaume Richard-Carpentier, MD.*

Abbreviations: Ara-C: Cytarabine; **D:** days; **G-CSF:** granulocyte colony-stimulating factor; **h:** hours; **IV:** intravenous; **mOS:** median overall survival; **ORR:** overall response rate; **PO:** *per os* (by mouth); **SC:** subcutaneous.

[A]Four hours after fludarabine infusion
[B]The idarubicin dose and duration differ for the newly diagnosed (8 mg/m^2 D4–6) and R/R (6 mg/m^2 D4–5) cohorts
[C]Venetoclax is given for 7 days each cycle and requires dose adjustment with concurrent administration of CYP3A4 inhibitors
[D]The 6-hour infusion of Ara-C is preceded by a short infusion (1 hour) of etoposide and followed, 3 hours later, by a bolus of mitoxantrone. Dosing for MEC may also be as follows: mitoxantrone 8 mg/m^2 IV x 5 days, etoposide 100 mg/m^2 x 5 days and cytarabine 1000 mg/m^2 x 5 days
[E]CR rate, not ORR
[F]Venetoclax requires dose adjustment with concurrent administration of CYP3A4 inhibitors
[G]Gilteritinib dose can be escalated up to 200 mg daily if no response after the first cycle

be preferred when a less toxic salvage strategy is desired, particularly in patients with more indolent disease kinetics, venetoclax-sensitive biology (e.g., *IDH1/2*-mutated AML), or when transplant eligibility is uncertain. Importantly, *TP53*-mutated and adverse-risk AML remain poor-risk entities regardless of the chosen strategy; in these cases, enrollment in clinical trials should be prioritized whenever feasible.[9,10,14,15]

Targeted Therapies

FLT3-mutated AML

In the phase III ADMIRAL trial, adults with R/R *FLT3*-mutated AML were randomized to receive gilteritinib or salvage chemotherapy (including regimens such as MEC and FLAG-IDA). Gilteritinib significantly improved OS (median 9.3 vs. 5.6 months; HR, 0.64; 95% confidence interval [CI], 0.49–0.83; P < 0.001) and achieved higher

remission rates (CR/complete remission with partial hematologic recovery [CRh] 34% vs. 15%) than chemotherapy, with a consistent benefit across subgroups. Importantly, more patients proceeded to HSCT in the gilteritinib arm, yet the survival advantage persisted even with censoring at the time of HSCT. Overall, toxicity was more favourable with gilteritinib, with lower rates of severe adverse events than with chemotherapy. These results established gilteritinib as a standard of care in R/R *FLT3*-mutated AML.[16]

Early-phase data support the combination of gilteritinib with venetoclax, with or without azacitidine, showing high response rates (around 70%–75%) and deep molecular responses. However, these data remain limited and investigational, and *FLT3* inhibitor-based combination therapies are not widely available in Canada outside clinical trials.[17,18]

IDH1- and *IDH2*-mutated AML

Although ivosidenib is available in Canada for the treatment of newly diagnosed *IDH1*-mutated AML in combination with azacitidine, ivosidenib and olutasidenib (*IDH1* inhibitors) and enasidenib (*IDH2* inhibitor) are not approved and available for the treatment of R/R AML.

In the phase I study of ivosidenib in *IDH1*-mutated R/R AML, clinically meaningful responses were observed in a heavily pre-treated population. Among patients with R/R disease, the combined CR and CRh rate was 30%, while the CR rate alone was 22%. The ORR was 39%, reflecting additional responses, such as CRi and morphologic leukemia-free state. The 18-month survival rate was 50% among patients with CR or CRh (median not reached at the data cut-off date).[19] Therefore, ivosidenib could be considered for patients with *IDH1*-mutated R/R AML, although access in Canada remains limited.

Outcomes with enasidenib are similar in *IDH2*-mutated R/R AML. However, it has been withdrawn from the Canadian market following negative results from the study by de Botton *et al.*, which failed to meet its primary endpoint.[20]

KMT2A Rearrangement (KMT2Ar) and *NPM1*-mutated AML

Menin inhibitors are a new class of targeted agents with activity in AML with *NPM1* mutations or *KMT2A* gene rearrangements located at 11q23. The first menin inhibitor, revumenib, was investigated in the AUGMENT-101 study, a phase I/II, open-label, multicentre clinical trial that led to its US Food and Drug Administration (FDA) approval.[21] The study included patients with *KMT2Ar* R/R acute leukemia and *NPM1*-mutated AML. Results from the phase II, registration-enabling portion in patients with *KMT2Ar* showed a CR/CRh rate of 23% and an ORR of 63%, allowing a quarter of patients in this study to proceed to HSCT.

Bleximenib is another potent and selective menin inhibitor currently under study as monotherapy or in combination regimens. In the phase I dose-finding study, bleximenib at the recommended phase II dose (RP2D) of 100 mg BID (twice/day) was associated with a composite CR (CR/CRh/CRi) rate of 40% and an ORR of 50%.[22] Menin inhibitors are currently only available in Canada through clinical trials, but will hopefully be approved and funded in the future.

HSCT and Donor Lymphocyte Infusion (DLI)

HSCT is considered the only potentially curative therapy for R/R AML. Most commonly, complete morphological remission with less than 5% bone marrow blasts is required before proceeding with HSCT to optimize post-transplant outcomes. Data show that the deeper the remission status is, the better the OS will be post-transplant.[23] However, this concept has been challenged by the ASAP trial, a multicentre, open-label, randomized controlled trial evaluating the non-inferiority of IC followed by immediate HSCT using reduced-intensity conditioning (RIC) compared with salvage chemotherapy intended to induce CR followed by HSCT. The trial showed no clear benefit of salvage chemotherapy and confirmation of CR before HSCT, while demonstrating higher rates of toxicity-related complications and longer hospitalization associated with salvage regimens. The 3-year OS was 59% (95% CI, 48–69) for patients undergoing IC with immediate RIC-based HSCT and 64% (95% CI, 49-76) for patients receiving salvage chemotherapy to achieve CR before proceeding to HSCT.[24]

DLI may also provide benefit as part of a salvage strategy in patients who relapse after HSCT. Reported OS rates at 1, 2, and 5 years were 67%, 34%, and 34%, respectively, among those receiving pre-emptive DLI, compared with 43%, 20%, and 20% in patients treated at overt relapse, as shown by Accorsi Buttini *et al*.[25]

Conclusion

AML is a heterogeneous disease, and responses to treatment vary based on disease features, with some patient subsets presenting with high rates of relapse. It is important to thoroughly characterize the genetic landscape at relapse, as this allows appropriate selection of salvage therapy, including targeted agents. Whenever possible, patients should be enrolled in clinical trials and referred for HSCT at the earliest opportunity. Lastly, it is of utmost importance to consider the patients' goals of care and to ensure early referral to the palliative care team to provide a holistic approach to this complex disease.

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SC=subcutaneous; NDMM=newly diagnosed multiple myeloma; ASCT=autologous stem cell transplant; D-VRd=DARZALEX® SC (daratumumab) + Velcade® (bortezomib) + Revlimid® (lenalidomide) + dexamethasone; VRd=Velcade® (bortezomib) + Revlimid® (lenalidomide) + dexamethasone; MRD=minimal residual disease; RR=risk ratio; CI=confidence interval; CR=complete response; NYHA=New York Heart Association; CBC=complete blood count; IgG=immunoglobulin G.

CEPHEUS Study parameters: A phase 3, open-label, multicentre, randomized, active-controlled study in patients with NDMM for whom ASCT was not planned as initial therapy or who were not eligible for ASCT. Patients were randomized 1:1 to receive D-VRd or VRd. All patients received eight 21-day cycles of VRd, consisting of SC bortezomib (1.3 mg/m^2 on Days 1, 4, 8, and 11), oral lenalidomide (25 mg on Days 1–14), and oral or intravenous dexamethasone (20 mg on Days 1, 2, 4, 5, 8, 9, 11, and 12 [Days 1, 4, 8, and 11 if aged >75 years or body mass index <18.5 kg/m^2], after which point bortezomib was discontinued per protocol and patients continued to receive 28-day cycles of Rd, consisting of oral lenalidomide (25 mg on Days 1–21) and oral dexamethasone (40 mg on Days 1, 8, 15, and 22 [20 mg weekly if aged >75 years or body mass index <18.5 kg/m^2]) until progression or unacceptable toxicity. Patients in the D-VRd group also received SC daratumumab (1800 mg co-formulated with recombinant human hyaluronidase PH20 (2000 U/mL) weekly in cycles 1–2, every 3 weeks in cycles 3–8), and every 4 weeks thereafter until progression or unacceptable toxicity.[1,2]

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