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REVIEW: CORONAVIRUS DISEASE (COVID-19) IN PATIENTS WITH HEMATOLOGIC MALIGNANCY

Introduction

The Coronavirus disease that emerged globally in 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It was first identified in December 2019, with rapid worldwide spread leading to a pandemic soon after. Three years later, although the virus now holds a diminished role in the public agenda, COVID-19 remains a real and present danger for patients with hematologic malignancy (HM).^{1,2} This paper provides an overview of the risks of COVID-19 in patients with HM, the effectiveness of vaccination, and management strategies in these vulnerable patients.

Outcomes of COVID-19 in Patients with Hematologic Malignancy

Patients with HM have impaired immune function due to the malignancy itself and as a consequence of HM treatments.

Immune dysfunction can affect all aspects of the immune system including disruptions to mucous membranes and other protective barriers; impaired innate immunity with reduced and/or dysfunctional granulocytes; and diminished adaptive immunity including low baseline antibody levels, delayed and/or reduced seroresponse, and impaired T cell response.³⁻⁶ These deficiencies result in increased vulnerability to infection, increased severity of illness and, in the case of COVID-19, prolonged viral clearance.⁷⁻¹⁰ B-cell depletion therapy, in particular, can greatly diminish seroresponse to vaccines and infection, and significantly increases the risk of severe COVID-19.³⁻⁵

At the outset of the pandemic, reports from Wuhan, China had already noted a more severe COVID-19 disease course and a higher case fatality rate in patients with HM infected with SARS-CoV-2.² In the numerous global reports that

followed, hospitalization rates were reported to be between 56% to 74%, intensive care unit (ICU) admission rates ranged from 10% to 24%, and case fatality rates ranged from 14% to 52% during the early waves of the virus.¹¹ A meta-analysis conducted during the early phase of the pandemic estimated a 34% risk of death in hospitalized patients with HM.¹ It is possible that selection bias augmented early estimates of COVID-19 mortality in patients with HM as initial reports were heavily skewed to hospitalized patients; however, with the passage of time it has become certain that patients with HM are at higher risk of serious morbidity, as well as mortality, than patients without cancer, and are even at higher risk than patients with solid tumors.¹¹ Predictors of worse outcomes in patients with HM include older age; specific subtypes of HM (higher risk for lymphoid malignancies and acute myeloid leukemia [AML]); higher comorbidity burden; having active malignancy; and receiving particular treatments (e.g., cellular therapy).¹²⁻¹⁴ During the last two years of the pandemic, the SARS-CoV-2 virus has continued to evolve leading to surges of new variants of concern (VOC) with increased transmissibility and immune escape. Despite this viral evolution, COVID-19 outcomes have improved over time,^{15,16} a trend that has also been observed among those with HM infected with SARS-CoV-2.^{17,18} For example, a recent study reporting on >1,500 patients with HM in the EPICOVIDEHA registry demonstrated reduced hospitalization rate (53% vs 73%), decreased ICU admission rate (10% vs 18%), and lower mortality (9% vs 31%) when compared to earlier in the pandemic.¹⁸ These improved outcomes are likely the result of several factors, including the natural evolution of SARS-CoV-2 leading to reduced virulence, immunologic protection from vaccination or past infection, and improved COVID-19-directed treatments. However, the relative contribution of each of these factors is difficult to tease out. Nevertheless, even in the contemporary era of COVID-19, it is widely recognized that patients with HM remain at increased risk of poor outcomes.¹¹

Prevention of SARS-CoV-2 Infection

Vaccination

One of the impressive success stories of the COVID-19 pandemic is the speed with which effective vaccinations were developed. Vaccines against SARS-CoV-2 became available in Canada in late 2020. Randomized controlled trials (RCTs) have demonstrated that all of the vaccines approved for use in Canada are highly efficacious in preventing severe COVID-19 infection,¹⁹⁻²¹ and real-world studies have confirmed that the vaccines are effective in preventing hospitalization and death.²² However, patients with cancer were excluded from vaccine RCTs and are under-represented in many population studies. Fortunately, large retrospective studies have recently been completed

which demonstrate that patients with HM also benefit from COVID-19 vaccination, although not to the same extent as patients without cancer, or even to the same extent as those with solid tumors.^{23,24}

Due to the technical challenges involved with assessing T cell response post-vaccination, most clinical studies have reported vaccine-mediated humoral response. It has been observed that breakthrough COVID-19 infections correlate with lower levels of anti-spike IgG and neutralizing antibodies, suggesting the importance of serologic response in protective immunity against COVID-19.²⁵ Patients with HM, particularly those with lymphoid malignancy and/or receiving B-cell depletion therapy, have impaired vaccine-mediated antibody responses, contributing to the vulnerability of this patient population.²⁶ Some of the lowest seroresponses have been observed in patients with chronic lymphocytic leukemia (CLL), irrespective of therapy. This has occurred among patients with prior or ongoing exposure to anti-CD20 therapy; in those receiving Bruton's tyrosine kinase inhibitors (BTKi's); and among recent cellular therapy recipients, including chimeric antigen receptor T-cell (CAR-T) therapy and stem cell transplant.²⁷⁻²⁹

Real-world studies have demonstrated that patients with cancer experience more rapid antibody waning than the general population following primary vaccination series,^{24,30} suggesting that earlier and greater booster doses may be required for ongoing protection from COVID-19. Recent clinical data from patients with cancer demonstrated that booster doses could seroconvert some patients who were previously negative, even among patients with lymphoid malignancies such as CLL. However, patients who received anti-CD20 therapy within one year of vaccination do not appear to derive the same benefit.^{27,31,32} For instance, a recent study by Shen et al evaluated seroconversion rates in patients with CLL and monoclonal B-cell lymphocytosis (MBL) following multiple (up to 8) COVID-19 vaccine doses; virtually all patients who were previously seronegative ultimately converted to seropositive.³³ Collectively, existing data support the use of repeated vaccine boosters to improve SARS-CoV-2 antibody levels among patients with HM.^{27,34} Moreover, despite poor humoral response to vaccination, up to 80% of patients treated with anti-CD20 therapy mounted a cellular T cell response; this may translate to some degree of protection even in the absence of antibody response.³⁵

Few clinical studies have addressed COVID-19 vaccine clinical effectiveness specifically in patients with HM. In a U.K. retrospective study conducted prior to the emergence of the Omicron variant, patients with cancer had 66% vaccine effectiveness for breakthrough infection; HM patients demonstrated reduced effectiveness.²⁴ In a matched comparative analysis using a population-based dataset from Ontario, including Omicron infections, patients with HM

had a higher risk of breakthrough infections and COVID-19-related poor outcomes versus noncancer controls and patients with solid cancers.²³ Booster vaccination reduced this risk, except for those who received anti-CD20 therapy in the year prior.³⁶

Nevertheless, although the relative risk of COVID-19 severe outcomes in patients with HM remains elevated, the absolute risk of death is much lower as compared with the pre-vaccination era³⁶; and vaccination remains the most important line of defense against COVID-19 for all patients, including those with HM. Strategies to improve immune responses include repeated vaccinations, maximizing vaccination prior to BCDT where possible, and revaccination three months following stem cell transplantation or CAR-T therapy.²⁵ Another important strategy is to optimize COVID-19 immunity among family members and caregivers of patients with HM via complete and up-to-date COVID-19 vaccination.

Pre-exposure Prophylaxis

Earlier in the pandemic, tailored antibodies directed against the SARS-CoV-2 spike protein were demonstrated to be a promising therapy to prevent severe COVID-19 in immunocompromised patients. Based on the PROVENT trial, the combination therapy tixagevimab/cilgavimab was approved as pre-exposure prophylaxis in patients with HM receiving immunosuppressive therapy such as anti-CD20 therapy and BTKi, as well as in transplant or CAR-T recipients.³⁷ Unfortunately, viral evolution has resulted in mutations in the SARS-CoV-2 spike protein, allowing immune escape from all commercially available monoclonal antibodies including tixagevimab-cilgavimab, and its use is no longer recommended.³⁸ However, research to develop monoclonal antibodies directed against more highly conserved portions of the virus is ongoing, and it is possible that monoclonal antibodies may prove to be useful again in the future.³⁹

Management

In addition to vaccines, new or newly re-purposed medical therapies have been developed to reduce the morbidity and mortality of COVID-19 in the outpatient and inpatient settings. Here-in, we provide a brief overview of COVID-19 management, current at the time of publication. With more than 3,000 trials of COVID-19 treatment registered,⁴⁰ the field of COVID-19 therapeutics is rapidly evolving, and we encourage readers to refer to rigorous, evidence-based guidelines available on this topic; in particular, the World Health Organization maintains a living, open-access guideline of COVID-19 therapeutics (<https://app.magicapp.org/#/guidelines>).⁴¹

Outpatient treatments

The first therapy approved by Health Canada for the treatment of COVID-19 was remdesivir, an intravenous

(IV) therapy. Remdesivir was approved by Health Canada on July 27, 2020, for treatment of SARS-CoV-2 pneumonia causing hypoxia. However, based on the PINETREE trial in non-hospitalized, unvaccinated patients at high risk for disease progression (5.3% had a cancer diagnosis), remdesivir's treatment indication was expanded to include non-hypoxic out-patients at risk of progression to severe COVID-19 in April, 2022. The PINETREE trial reported an 87% relative risk reduction (RRR) in hospitalization or death vs placebo when remdesivir was administered within seven days of symptoms onset.⁴² Despite demonstrated efficacy, the three-day IV regimen poses logistical challenges for the outpatient population. As well, evidence of benefit in vaccinated individuals, or in those with natural immunity, is sparse and the benefits are likely lower in this setting. Nevertheless, real-world evidence suggests that remdesivir use is associated with decreased mortality in patients with HM.⁴³

Ritonavir-boosted nirmatrelvir is an oral protease inhibitor that inhibits the SARS-CoV-2 protease critical for viral replication. It was approved by Health Canada on January 17, 2022, for the treatment of patients with mild-to-moderate COVID-19 based on the EPIC-HR trial in high-risk, unvaccinated individuals. The trial reported reduced COVID-19 hospitalizations/death from 6.4% to 0.8% vs placebo.⁴⁴ Although prospective data on the effectiveness of nirmatrelvir/ritonavir is lacking among vaccinated or naturally immunized individuals, due to its ease of use it has rapidly become first-line therapy for out-patients at risk of severe COVID-19. At the time of this writing, a 5 day course of nirmatrelvir/ritonavir is indicated as first-line treatment for symptomatic outpatients with mild-to-moderate COVID-19 presenting within 5 days of symptom onset. Of note, its use is complicated by drug-drug interactions due to ritonavir-mediated CYP3A4 inhibition. Numerous drugs used to treat HM have important interactions with ritonavir requiring either dose adjustments or avoidance. Detailed information on drug interactions with nirmatrelvir/ritonavir is available via open-access resources including the Liverpool COVID-19 Drug Interaction Checker (<https://www.covid19-druginteractions.org/checker>)⁴⁵ and the University Health Network drug-drug oncology interaction checker (<https://www.antimicrobialstewardship.com/paxlovid-ddi-oncology>).⁴⁶ Nirmatrelvir-ritonavir requires dosing modifications in cases of renal impairment, as well as avoidance in patients with severe hepatic impairment (<https://doi.org/10.47326/ocsat.2022.03.58.3.0>).

Three SARS-CoV-2 neutralizing antibody therapies have been authorized by Health Canada for reducing the risk of severe COVID-19 in non-hospitalized, high risk patients: bamlanivimab, casirivimab plus imdevimab, and sotrovimab. However, similar to prophylactic monoclonal antibody treatment, these monoclonal antibodies are no longer

recommended as dominant circulating strains of SARS-Co-V2 in Canada have reduced susceptibility to these agents.⁴⁷

In summary, nirmatrelvir-ritonavir (oral) and remdesivir (IV) are the two treatment options currently recommended for ambulatory patients with mild-to-moderate COVID-19 in Canada (**Figure 1**).^{48,49} Both of these agents require initiation shortly after symptom onset in order to be effective. Oncologists and hematologists can play a key role in counselling patients with HM regarding how to recognize the symptoms of COVID-19 and the importance of prompt testing to facilitate early COVID-19 treatment. New therapeutic strategies are currently under active evaluation, including oral analogues of remdesivir⁵⁰ and a single dose of subcutaneous pegylated interferon lambda,⁵¹ and may become available in the future.

Inpatient treatments

A number of important inpatient therapies have been developed for those with severe-to- critical COVID-19 (**Figure 1**). Patients with mild-to-moderate COVID-19, hospitalized for non-COVID-19 indications, should be treated in the same manner as outpatients with COVID-19, with either a three-day course of IV remdesivir or a five-day course of nirmatrelvir/ritonavir. Patients admitted with severe COVID-19 requiring supplemental oxygen but not requiring invasive ventilation may benefit from a

five- to ten-day course of IV remdesivir.⁵² A recent meta-analysis of this population suggests a slight mortality reduction and decreased need for mechanical ventilation.⁵³ A ten-day course of dexamethasone 6 mg is recommended for the treatment of COVID-19 in hospitalized patients who require non-invasive or high-flow supplemental oxygen, given the mortality benefit demonstrated in the RECOVERY trial.⁵⁴

For patients with critical COVID-19, particularly those with elevated inflammatory markers, the addition of the anti-interleukin 6 (IL-6) monoclonal antibody tocilizumab or Janus kinase (JAK) inhibitor baricitinib should be considered.⁵⁵ None of the trials of the above-mentioned COVID-19 therapeutics included patients with HMs; nonetheless, most experts recommend that these patients be treated similarly to those without HMs with severe COVID-19, with the caveat that treating clinicians should be mindful of the further immunosuppressive effects of these therapies and the potential implications for infectious complications.

Although case series have reported convalescent plasma effectiveness in patients with HM, its routine use is controversial as large clinical trials have failed to demonstrate efficacy and its use is operationally challenging.¹¹



COVID-19 outcomes in patients with blood cancer



While COVID-19 morbidity and mortality is decreasing, it remains 2-fold higher in patients with blood cancer compared to no cancer and solid cancer



Predictors of worse outcomes:
age $\geq 60-75$, comorbidity burden, active cancer, subtype (lymphoma, CLL, myeloma, AML)



SARS-CoV-2 vaccination is effective in patients with blood cancer



Immunologic response:
Humoral response 40-77%
Cellular response 53-79%

Vaccine effectiveness:
Infection: 52.9% for blood cancer (65.5% all cancer)
Hospitalization: 84.5% (all cancer)
Mortality: 93.5% (all cancer)



High risk for blunted vaccine response:
Lymphoma/CLL, BTKi, anti-CD20 treatment, ASCT, CAR-T



Patient with hematologic malignancy with SARS-CoV-2 infection

Mild - Mod COVID-19

Nirmatrelvir 300 mg +
Ritonavir 100 mg
PO BID for 5 d
(within 5 d Sx onset)

Remdesivir 200 mg IV D1
Remdesivir 100 mg IV D2-D3
(within 7d Sx onset)

Severe COVID-19

Dexamethasone 6 mg for
10 d

Remdesivir 200 mg IV D1
Remdesivir 100 mg D2-D5

Critical COVID-19

Dexamethasone 6 mg for
10 d

Tocilizumab 8 mg/kg IV x 1
(max of 800mg)
OR
Baricitinib 4 mg PO for 14 d

Figure 1. Overview of COVID-19 outcomes, vaccine efficacy and treatment strategies for patients with hematologic malignancy; courtesy of Inna Gong, MD and Lisa Hicks, MD

For non-critically ill, hospitalized patients, therapeutic intensity anticoagulation with heparin or low molecular weight heparin (LMWH) is suggested over prophylactic intensity, based on evidence from three RCTs.⁵⁶ For critically ill patients, prophylactic intensity anticoagulation is recommended.⁵⁶

Conclusion

Clinicians caring for patients with HM have an important role to play as the COVID-19 pandemic stretches into its fourth year. Despite major scientific advances, patients with HM remain uniquely vulnerable to hospitalization, morbidity and mortality from COVID-19. Vaccination is the most important defence against COVID-19, even among patients with HM who may have an attenuated or initially absent vaccine response. The benefits of vaccination for patients with HM have been shown in real-world population-based studies, and encouraging patients

with HM, their household contacts, and their caregivers (including healthcare workers) to stay current with vaccination is an important part of contemporary HM care. Teaching patients how to recognize COVID-19 infection, as well as the importance of early testing to facilitate outpatient anti-viral treatment, is also critical. Finally, one of the most important things that oncologists can undertake to reduce COVID-19 morbidity and mortality is advocacy. As COVID-19 retreats from the front pages of newspapers it is incumbent upon experts in HM to remind healthcare, civic and government leaders that COVID-19 remains a threat for our patients.

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References

- Vijenthira A, Gong IY, Fox TA, Booth S, Cook G, Fattizzo B, Martin-Moro F, Razanamahery J, Riches JC, Zwicker J, Patel R. Outcomes of patients with hematologic malignancies and COVID-19: a systematic review and meta-analysis of 3377 patients. *Blood*. 2020 Dec 17;136(25):2881-92.
- He W, Chen L, Chen L, Yuan G, Fang Y, Chen W, Wu D, Liang B, Lu X, Ma Y, Li L. COVID-19 in persons with hematological cancers. *Leukemia*. 2020 Jun;34(6):1637-45.
- Candoni A, Pizzano U, Fabris M, Curcio F, Fanin R. Seroconversion and kinetic of anti SARS-CoV-2 antibodies in 25 patients with hematological malignancies who recovered from SARS-CoV-2 infection. *Hematological Oncology*. 2021 Aug;39(3):428.
- Cattaneo C, Cancelli V, Imberti L, Dobbs K, Sottini A, Pagani C, Belotti A, Re A, Anastasia A, Quaresima V, Tucci A. Production and persistence of specific antibodies in COVID-19 patients with hematologic malignancies: role of rituximab. *Blood Cancer Journal*. 2021 Sep 14;11(9):151.
- Passamonti F, Romano A, Salvini M, Merli F, Porta MG, Bruna R, Coviello E, Romano I, Cairolì R, Lemoli R, Farina F. COVID-19 elicits an impaired antibody response against SARS-CoV-2 in patients with hematological malignancies. *British Journal of Haematology*. 2021 Nov;195(3):371-7.
- Russell CD, Lone NI, Baillie JK. Comorbidities, multimorbidity and COVID-19. *Nature Medicine*. 2023 Feb 16;1-07.
- Abdul-Jawad S, Bai L, Alaguthurai T, et al. Acute Immune Signatures and Their Legacies in Severe Acute Respiratory Syndrome Coronavirus-2 Infected Cancer Patients. *Cancer Cell*. 2021;39(2):257-275.e256.
- Bange EM, Han NA, Wileyto P, Kim JY, Gouma S, Robinson J, Greenplate AR, Hwee MA, Porterfield F, Owoyemi O, Naik K. CD8+ T cells contribute to survival in patients with COVID-19 and hematologic cancer. *Nature Medicine*. 2021 Jul;27(7):1280-9.
- Bilich T, Roerden M, Maringer Y, Nelde A, Heimann JS, Dubbelaar ML, Peter A, Hörber S, Bauer J, Rieth J, Wacker M. Preexisting and Post-COVID-19 Immune Responses to SARS-CoV-2 in Patients with CancerImmune Responses to SARS-CoV-2 in Patients with Cancer. *Cancer Discovery*. 2021 Aug 11;11(8):1982-95.
- Mansi L, Spehner L, Daguindau E, Bouiller K, Almotlak H, Stein U, Bouard A, Kim S, Klajer E, Jary M, Meynard G. Study of the SARS-CoV-2-specific immune T-cell responses in COVID-19-positive cancer patients. *European Journal of Cancer*. 2021 Jun 1;150:1-9.
- Langerbeins P, Hallek M. COVID-19 in patients with hematologic malignancy. *Blood*. 2022 May 1
- Lee LY, Cazier JB, Starkey T, Briggs SE, Arnold R, Bisht V, Booth S, Campton NA, Cheng VW, Collins G, Curley HM. COVID-19 prevalence and mortality in patients with cancer and the effect of primary tumour subtype and patient demographics: a prospective cohort study. *The Lancet Oncology*. 2020 Oct 1;21(10):1309-16.
- Pagano L, Salmanton-García J, Marchesi F, Busca A, Corradini P, Hoenigl M, Klimko N, Koehler P, Pagliuca A, Passamonti F, Verga L. COVID-19 infection in adult patients with hematological malignancies: a European Hematology Association Survey (EPICOVIDEHA). *Journal of Hematology & Oncology*. 2021 Oct 14;14(1):168.
- Passamonti F, Cattaneo C, Arcaini L, Bruna R, Cavo M, Merli F, Angelucci E, Krampera M, Cairolì R, Della Porta MG, Fracchiolla N. Clinical characteristics and risk factors associated with COVID-19 severity in patients with hematological malignancies in Italy: a retrospective, multicentre, cohort study. *The Lancet Haematology*. 2020 Oct 1;7(10):e737-45.
- Asch DA, Sheils NE, Islam MN, Chen Y, Werner RM, Buresh J, Doshi JA. Variation in US hospital mortality rates for patients admitted with COVID-19 during the first 6 months of the pandemic. *JAMA Internal Medicine*. 2021 Apr 1;181(4):471-8.
- Nyberg T, Ferguson NM, Nash SG, Webster HH, Flaxman S, Andrews N, Hinsley W, Bernal JL, Kall M, Bhatt S, Blomquist P. Comparative analysis of the risks of hospitalisation and death associated with SARS-CoV-2 omicron (B.1.1.529) and delta (B.1.617.2) variants in England: a cohort study. *The Lancet*. 2022 Apr 2;399(10332):1303-12.
- Niemann CU, da Cunha-Bang C, Helleberg M, Ostrowski SR, Brieghel C. Patients with CLL have a lower risk of death from COVID-19 in the Omicron era. *Blood, The Journal of the American Society of Hematology*. 2022 Aug 4;140(5):445-50.
- Pagano L, Salmanton-García J, Marchesi F, Blennow O, da Silva MG, Glenhøj A, van Doesum J, Bilgin YM, Lopez-García A, Federico IT, Rodrigues RN. Breakthrough COVID-19 in vaccinated patients with hematologic malignancies: results from EPICOVIDEHA survey. *Blood*. 2022 Sep 22.
- Heath PT, Galiza EP, Baxter DN, Boffito M, Browne D, Burns F, Chadwick DR, Clark R, Cosgrove C, Galloway J, Goodman AL. Safety and efficacy of NVX-CoV2373 Covid-19 vaccine. *New England Journal of Medicine*. 2021 Sep 23;385(13):1172-83.
- Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, Diemert D, Spector SA, Rouphael N, Creech CB, McGettigan J. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *New England Journal of Medicine*. 2021 Feb 4;384(5):403-16.
- Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, Perez JL, Pérez Marc G, Moreira ED, Zerbini C, Bailey R. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *New England Journal of Medicine*. 2020 Dec 31;383(27):2603-15.
- Zheng C, Shao W, Chen X, Zhang B, Wang G, Zhang W. Real-world effectiveness of COVID-19 vaccines: a literature review and meta-analysis. *International Journal of Infectious Diseases*. 2022 Jan 1;114:252-60.
- Gong IY, Vijenthira A, Powis M, Calzavara A, Patrikar A, Sutradhar R, Hicks LK, Wilton D, Singh S, Kryczanowska MK, Cheung MC. Association of COVID-19 vaccination with breakthrough infections and complications in patients with cancer. *JAMA Oncology*. 2023 Mar 1;9(3):386-94.
- Lee LY, Starkey T, Ionescu MC, Little M, Tilby M, Tripathy AR, McKenzie HS, Al-Hajji Y, Barnard M, Benny L, Burnett A. Vaccine effectiveness against COVID-19 breakthrough infections in patients with cancer (UKCCFEP): a population-based test-negative case-control study. *The Lancet Oncology*. 2022 Jun 1;23(6):748-57.
- Bergwerk M, Gonen T, Lustig Y, Amit S, Lipsitch M, Cohen C, Mandelboim M, Levin EG, Rubin C, Indenbaum V, Tal I. Covid-19 breakthrough infections in vaccinated health care workers. *New England Journal of Medicine*. 2021 Oct 14;385(16):1474-84.
- Thakkar A, Gonzalez-Lugo JD, Goradia N, Gali R, Shapiro LC, Pradhan K, Rahman S, Kim SY, Ko B, Sica RA, Kornblum N. Seroconversion rates following COVID-19 vaccination among patients with cancer. *Cancer Cell*. 2021 Aug 9;39(8):1081-90.
- Greenberger LM, Saltzman LA, Senefeld JW, Johnson PW, DeGennaro LJ, Nichols GL. Anti-spike antibody response to SARS-CoV-2 booster vaccination in patients with B cell-derived hematologic malignancies. *Cancer Cell*. 2021 Oct 11;39(10):1297-9.
- Greenberger LM, Saltzman LA, Senefeld JW, Johnson PW, DeGennaro LJ, Nichols GL. Antibody response to SARS-CoV-2 vaccines in patients with hematologic malignancies. *Cancer Cell*. 2021 Aug 9;39(8):1031-3.
- Lim SH, Campbell N, Johnson M, Joseph-Pietras D, Collins GP, O'Callaghan A, Fox CP, Ahearne M, Johnson PW, Goldblatt D, Davies AJ. Antibody responses after SARS-CoV-2 vaccination in patients with lymphoma. *The Lancet Haematology*. 2021 Aug 1;8(8):e542-4.
- Levin EG, Lustig Y, Cohen C, Fluss R, Indenbaum V, Amit S, Doolman R, Asraf K, Mendelson E, Ziv A, Rubin C. Waning immune humoral response to BNT162b2 Covid-19 vaccine over 6 months. *New England Journal of Medicine*. 2021 Dec 9;385(24):e84.
- Shapiro LC, Thakkar A, Campbell ST, Forest SK, Pradhan K, Gonzalez-Lugo JD, Quinn R, Bhagat TD, Choudhary GS, McCort M, Sica RA. Efficacy of booster doses in augmenting waning immune responses to COVID-19 vaccine in patients with cancer. *Cancer Cell*. 2022 Jan 10;40(1):3-5.
- Kohn M, Delord M, Chbat M, Guemriche A, Merabet F, Roupie AL, Lombion N, Farhat H, Longval T, Cabannes-Hamy A, Lambert J. A third anti-SARS-CoV-2 mRNA dose does not overcome the pejorative impact of anti-CD20 therapy and/or low immunoglobulin levels in patients with lymphoma or chronic lymphocytic leukemia. *Haematologica*. 2022 Jun 6;107(6):1454.
- Shen Y, Freeman JA, Holland J, Naidu K, Solterbeck A, Van Bilsen N, Downe P, Kerridge I, Wallman L, Akerman A, Aggarwal A. Multiple COVID-19 vaccine doses in CLL and MBL improve immune responses with progressive and high seroconversion. *Blood, The Journal of the American Society of Hematology*. 2022 Dec 22;140(25):2709-21.
- Haggenburg S, Hofsch Q, Lissenberg-Witte BI, Broers AE, Van Doesum JA, Van Binnendijk RS, Den Hartog G, Bhoekhan MS, Haverkate NJ, Burger JA, Bouhuijs JH. Antibody response in immunocompromised patients with hematologic cancers who received a 3-dose mRNA-1273 vaccination schedule for COVID-19. *JAMA oncology*. 2022 Oct 1;8(10):1477-83.
- Jiménez M, Roldán E, Fernández-Naval C, Villacampa G, Martínez-Gallo M, Medina-Gil D, Peralta-Garzón S, Pujadas G, Hernández C, Pagès C, Gironella M. Cellular and humoral immunogenicity of the mRNA-1273 SARS-CoV-2 vaccine in patients with hematologic malignancies. *Blood Advances*. 2022 Feb 8;6(3):774-84.
- Barda N, Dagan N, Cohen C, Hernán MA, Lipsitch M, Kohane IS, Reis BY, Balicer RD. Effectiveness of a third dose of the BNT162b2 mRNA COVID-19 vaccine for preventing severe outcomes in Israel: an observational study. *The Lancet*. 2021 Dec 4;398(10316):2093-100.
- Levin MJ, Ustianowski A, De Wit S, Launay O, Avila M, Templeton A, Yuan Y, Seegobin S, Ellery A, Levinson DJ, Ambery P. Intramuscular AZD7442 (tisagevimab-cilgavimab) for prevention of COVID-19. *New England Journal of Medicine*. 2022 Jun 9;386(23):2188-200.
- Cox M, Peacock TP, Harvey WT, Hughes J, Wright DW. COVID-19 Genomics UK (COG-UK) Consortium, Willett BJ, Thomson E, Gupta RK, Peacock SJ, Robertson DL. SARS-CoV-2 variant evasion of monoclonal antibodies based on in vitro studies. *Nature Reviews Microbiology*. 2023 Feb 21(2):112-24.
- Dacon C, Tucker C, Peng L, Lee CC, Lin TH, Yuan M, Cong Y, Wang L, Purser L, Williams JK, Pyo CW. Broadly neutralizing antibodies target the coronavirus fusion peptide. *Science*. 2022 Aug 12;377(6607):728-35.
- Living Systematic Review. Vol. 2023: Infectious Diseases Data Observatory.
- WHO. Therapeutics and COVID-19: living guideline. Vol. 2023.
- Gottlieb RL, Vaca CE, Paredes R, Mera J, Webb BJ, Perez G, Oguchi G, Ryan P, Nielsen BU, Brown M, Hidalgo A. Early remdesivir to prevent progression to severe Covid-19 in outpatients. *New England Journal of Medicine*. 2022 Jan 27;386(4):305-15.
- Levy I, Lavi A, Zimran E, Grisariu S, Aumann S, Ichaki G, Berger T, Raanani P, Harel R, Aviv A, Lavi N. COVID-19 among patients with hematological malignancies: a national Israeli retrospective analysis with special emphasis on treatment and outcome. *Leukemia & Lymphoma*. 2021 Dec 6;62(14):3384-93.
- Hammond J, Leister-Tebbe H, Gardner A, Abreu P, Bao W, Wisemandle W, Baniecki M, Hendrick VM, Damlé B, Simón-Campos A, Pypstra R. Oral nirmatrelvir for high-risk, nonhospitalized adults with Covid-19. *New England Journal of Medicine*. 2022 Apr 14;386(15):1397-408.
- COVID-19 drug interactions. Vol. 2023: Liverpool COVID-19 Interactions Checker. <https://www.covid19-druginteractions.org/>. Accessed April 4, 2023.
- Nirmatrelvir/Ritonavir (Paxlovid) Management of Drug-Drug Interactions in Oncology. Vol. 2023: University Health Network. <https://www.antimicrobialstewardship.com/paxlovid-ddi-oncology>. Accessed April 4, 2023.
- Iketani S, Liu L, Guo Y, Liu L, Chan JF, Huang Y, Wang M, Luo Y, Yu J, Chu H, Chik KK. Antibody evasion properties of SARS-CoV-2 Omicron sublineages. *Nature*. 2022 Apr 21;604(7906):553-6.
- Li P, Wang Y, Lavrijsen M, Lamers MM, de Vries AC, Rotter RJ, Bruno MJ, Peppelenbosch MP, Haegmans BL, Pan Q. SARS-CoV-2 Omicron variant is highly sensitive to molnupiravir, nirmatrelvir, and the combination. *Cell Research*. 2022 Mar;32(3):322-4.
- Takashita E, Kinoshita N, Yamayoshi S, Sakai-Tagawa Y, Fujisaki S, Ito M, Iwatsuki-Horimoto K, Chiba S, Halfmann P, Nagai H, Saito M. Efficacy of antibodies and antiviral drugs against Covid-19 omicron variant. *New England Journal of Medicine*. 2022 Mar 10;386(10):995-8.
- Cao Z, Gao W, Bao H, Feng H, Mei S, Chen P, Gao Y, Cui Z, Zhang Q, Meng X, Gui H. VV116 versus nirmatrelvir-ritonavir for oral treatment of Covid-19. *New England Journal of Medicine*. 2023 Feb 2;388(5):406-17.
- Reis G, Moreira Silva EA, Medeiros Silva DC, Thabane L, Campos VH, Ferreira TS, Santos CV, Nogueira AM, Almeida AP, Savassi LC, Figueiredo-Neto AD. Early treatment with pegylated interferon lambda for covid-19. *New England Journal of Medicine*. 2023 Feb 9;388(6):518-28.
- Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, Hohmann E, Chu HY, Luetkemeyer A, Kline S, Lopez de Castilla D. Remdesivir for the treatment of Covid-19. *New England Journal of Medicine*. 2020 Nov 5;383(19):1813-26.
- Amstutz A, Speich B, Mentré F, Rueegg CS, Belhadi D, Assoumou L, Burdet C, Murthy S, Dodd LE, Wang Y, Tikkenin KA. Effects of remdesivir in patients hospitalised with COVID-19: a systematic review and individual patient data meta-analysis of randomised controlled trials. *The Lancet Respiratory Medicine*. 2023 Feb 21.
- RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with Covid-19. *New England Journal of Medicine*. 2021 Feb 25;384(8):693-704.
- Kalil AC, Patterson TF, Mehta AK, Tomashek KM, Wolfe CR, Ghazaryan V, Marconi VC, Ruiz-Palacios GM, Hsieh L, Kline S, Tapson V. Baricitinib plus remdesivir for hospitalized adults with Covid-19. *New England Journal of Medicine*. 2021 Mar 4;384(9):795-807.
- ASH Guidelines on Use of Anticoagulation in Patients with COVID-19. Vol. 2023: American Society of Hematology.

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CELLULAR THERAPY IN CLL/iNHL: THERAPEUTIC AGENTS IN THE PIPELINE

Introduction

Advanced cellular therapies have been introduced in Canada over the past two years. Chimeric antigen receptor (CAR) T-cell therapy is the current standard of care for third-line large B-cell lymphoma (LBCL), relapsed/refractory (RR) acute lymphoblastic leukemia (ALL) in patients <26 years old³ and, more recently, in third-line mantle cell lymphoma.⁴ These novel therapies are now gaining more prominence in the treatment of LBCL with recent FDA approval for the second line in patients eligible for stem cell transplant, based on recent Phase 3 trials.^{5,6} Another class of novel immunotherapy agents are bispecific T-cell engagers (BiTEs) which have been studied in many B-cell malignancies but are not yet approved in Canada.

The indolent non-Hodgkin's lymphoma (iNHL) and chronic lymphocytic leukemia (CLL) landscape have been evolving over the past few years with many novel therapies being studied and becoming available. However, patients with RR iNHL, as well as patients using Bruton tyrosine kinase (BTK) and B-cell lymphoma-2 (BCL2) inhibitors for refractory CLL continue to have an unmet need for treatment. This article will focus on cellular therapy that will likely be available for use by Canadian clinicians in the near future to treat patients with iNHL and CLL.

Cellular Therapy in Indolent NHL

iNHL represents at least 35% of new cases of non-Hodgkin's lymphoma in the United States; follicular lymphoma represents the most common of these cases. iNHLs are likely underdiagnosed and their incidence may be even higher, given that a significant number of patients

with the disease are asymptomatic.⁷ The clinical course of the majority of iNHLs is very heterogeneous and many patients experience extended survival.⁸ However, many patients will likely need treatment at some point based on the clinical evolution of the disease. Particularly in follicular lymphoma, it is well known that progressive disease in the first 24 months (POD24) following standard chemoimmunotherapy is associated with a poor prognosis.⁹

Axicabtagene ciloleucel (axi-cel) and tisagenlecleucel (tisa-cel) are currently available in the United States and Europe and will likely be available in Canada in the near future. Axi-cel was approved based on ZUMA-5, a single arm, Phase 2 clinical trial.¹⁰ In this trial, both follicular (n=124) and marginal zone (n= 24) lymphomas were included after having failed at least two prior lines of therapy (median of three). The majority of the cohort (55%) had POD24. Despite this, the overall response rate (ORR) was 92%, with a 74% complete response (CR) rate. In the updated analysis, the 18-month progression-free survival (PFS) and overall survival (OS) were 65% and 87%, respectively. Tisa-cel was approved outside of Canada based on the ELARA study.¹¹ ELARA was also a Phase 2, single arm clinical study investigating patients having received at least two prior lines of therapy (median of 4); however, it included only follicular lymphoma. The majority of the cohort (63%) also experienced POD24 and 78% were refractory to their last line of treatment. The ORR was impressive at 92%, with a 75% CR rate. The reported 12-month PFS was 67%.

Rapid access to treatment for the high-risk disease population is the area requiring the greatest advocacy. For

the high-risk population with POD24, Axi-cel was associated with an impressive ORR of 92% with a 75% CR rate and an 18-month duration of response of 60%.¹² With Tisa-cel, the CR rate was 59% and the 12-month PFS was 61%.¹³

The primary advantage of CAR T-cell therapy is its single infusion treatment. However, it has a unique toxicity profile as compared with other therapies; the two initial side effects are cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). In LBCL, CRS was reported in 58%-93% patients, with 13%-22% Grade ≥ 3 , and ICANS in 21%-64% of patients, with 12%-28% Grade ≥ 3 .^{1,2,14} In iNHL, the CRS rate was lower, at 49%-82% and 0%-7% Grade ≥ 3 . ICANS was no different, with a rate of 4.1%-59% and 1%-19% Grade ≥ 3 .^{10,11} Cytopenias, B-cell aplasia and infections are additional moderate to long-term side effects that must be considered after CAR T-cell therapy infusion.

BiTEs are another novel form of immunotherapy. The mechanism of action of these antibody therapies is based on recognition of a specific target on tumor cells with another binding site for engaging T-cells.¹⁵ Current BiTEs target CD20 and CD3; mosunetuzumab is the most advanced in terms of access process.¹⁶ Other BiTEs have been investigated in B-cell malignancies, in recently-published Phase 1 clinical studies evaluating glofitamab, epcoritamab and odronextamab.¹⁷⁻¹⁹ BiTEs have the advantage of being rapidly available compared to CAR T-cell therapy which requires apheresis of a fresh product, and a manufacturing time which reduces the time to therapy from 4-6 weeks to only 1-2 weeks at the most.

A Phase 2, single arm mosunetuzumab trial was recently published.¹⁶ Only follicular lymphomas with at least two prior lines of therapy (median 3) were included. Prior CAR

T-cell treatment was not excluded, but represented only 3% of the cohort. Fifty-two percent of the study cohort had POD24. As with the majority of BiTEs, CRS is the most common adverse event; however, it can be mitigated by the use of scheduled titration. Mosunetuzumab requires an infusion every three weeks until progression. In this clinical trial, ORR was 80%, with a 60% CR rate. CRS was confined primarily to cycle 1 with a 44% incidence in all grades but only 2% Grades 3/4. Despite a short follow-up, no unexpected major adverse events have been reported. The key characteristics of the available Phase 2 clinical trials are summarized in **Table 1**.

Cellular Therapy in Chronic Lymphocytic Leukemia (CLL)

Cellular therapy in CLL is still in its early phase. CAR T-cell and BiTEs therapy are emerging as promising treatment strategies for patients who are refractory to both BTK and BCL2 inhibitors.

Although currently there is no product approved for commercial use in Canada, the United States or Europe, several patients with CLL have been treated with cellular therapy for more than 10 years. A recent report described the characteristics of two patients who have been in remission since the infusion of their CD-19 directed CAR T-cell therapy. Data on lisocabtagene-maraleucel (liso-cel), a CD-19 directed CAR T-cell therapy which has published data on LBCL, but is not currently available in Canada in any indication, has recently been published for patients with CLL. This Phase 1 study (TRANSCEND CLL 004), involving 23 patients with standard and high-risk disease and 2-3 prior lines of therapy (including a BTK inhibitor) showed an 82% ORR and a 45% CR or CR with incomplete marrow recovery (CRi) rate. In the cohort of patients who progressed on both BTK and BCL2 inhibitors, the highest

Therapy	Phase	Histology	N	ORR (%)	CRR (%)	Median DOR (months)	Median PFS (months)	Median OS (months)
Axicabtagene ciloleucel ¹⁰	II	FL/MZL	109	92	76	NR 18 months DOR was 66%	NR 18-month PFS was 65%	NR 18-month OS was 87%
Tisagenlecleucel ¹¹	II	FL	94	87	69	NR Among patients with CR 9-month DOR was 87%	NR 12-month PFS was 67%	NR
Mosunetuzumab ¹⁶	II	FL	90	80	60	23	18	NR 18-month OS was 90%

Table 1. Phase 2 studies of cellular therapies in iNHL; courtesy of Christopher Lemieux, MD
DOR: Duration of response, FL: Follicular lymphoma, MZL: Marginal zone lymphoma, NR: not reached, PFS: progression free survival, OS: Overall survival.

ORR was 80% (60% CR/CRi); 78% achieved undetectable minimal residual disease in the blood and 67% in the marrow, which appears to be promising for those patients with a current unmet need.²⁰ In terms of toxicity, CRS occurred in 74% (9% Grade 3) of the cohort and ICANS occurred in 39% (22% Grades 3/4), which is higher than that seen in the LBCL cohort.¹⁴ Results of the Phase 2 trial will have to be followed (NCT03331198). Other early phase trials have shown comparable results in this population.²¹⁻²³ The usefulness of using a BTK inhibitor throughout the CAR T-cell treatment process remains to be determined.

The development of BiTEs in CLL currently focuses on CD3-CD20 dual targeting. Epcoritamab (NCT04623541) and mosunetuzumab (NCT05091424) studies are ongoing. Preliminary results from the EPCORE CLL-1 trial have been previously presented, however, only five patients were assessed for responses.²⁴

Conclusion

Cellular therapy has been emerging in B-cell malignancy, iNHL and CLL over the past decade. It is hoped that these novel therapies will become available for Canadian patients in the near future. Despite showing high response rates, longer-term follow up of these trial cohorts will elucidate the durability of response of these novel agents. In addition, defining the patient population for which these therapies should be available in the future might become a factor in payors' decision-making process.

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References

- Neelapu SS, Locke FL, Bartlett NL, Lekakis LJ, Miklos DB, Jacobson CA, Braunschweig I, Ohnwole OO, Siddiqi T, Lin Y, Timmerman JM. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. *New England Journal of Medicine*. 2017 Dec 28;377(26):2531-44.
- Schuster SJ, Bishop MR, Tam CS, Waller EK, Borchmann P, McGuirk JP, Jäger U, Jaglowski S, Andreadis C, Westin JR, Fleury I. Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. *New England Journal of Medicine*. 2019 Jan 3;380(1):45-56.
- Maude SL, Laetsch TW, Buechner J, Rives S, Boyer M, Bittencourt H, Bader P, Verneis MR, Stefanski HE, Myers GD, Qayed M. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. *New England Journal of Medicine*. 2018 Feb 1;378(5):439-48.
- Wang M, Munoz J, Goy A, Locke FL, Jacobson CA, Hill BT, Timmerman JM, Holmes H, Jaglowski S, Flinn IW, McSweeney PA. KTE-X19 CAR T-cell therapy in relapsed or refractory mantle-cell lymphoma. *New England journal of medicine*. 2020 Apr 2;382(14):1331-42.
- Locke FL, Miklos DB, Jacobson CA, Perales MA, Kersten MJ, Ohnwole OO, Ghobadi A, Rapoport AP, McGuirk J, Pagel JM, Muñoz J. Axicabtagene ciloleucel as second-line therapy for large B-cell lymphoma. *New England Journal of Medicine*. 2022 Feb 17;386(7):640-54.
- Kamdar M, Solomon SR, Arnason J, Johnston PB, Glass B, Bachanova V, Ibrahim S, Mielke S, Mutsaers P, Hernandez-Ilizaliturri F, Izutsu K. Lisocabtagene maraleucel versus standard of care with salvage chemotherapy followed by autologous stem cell transplantation as second-line treatment in patients with relapsed or refractory large B-cell lymphoma (TRANSFORM): results from an interim analysis of an open-label, randomised, phase 3 trial. *The Lancet*. 2022 Jun 18;399(10343):2294-308.
- Morton LM, Wang SS, Devesa SS, Hartge P, Weisenburger DD, Linet MS. Lymphoma incidence patterns by WHO subtype in the United States, 1992-2001. *Blood*. 2006 Jan 1;107(1):265-76.
- Bachy E, Seymour JF, Feugier P, Offner F, López-Guillermo A, Belada D, Xerri L, Catalano JV, Brice P, Lemonnier F, Martin A. Sustained progression-free survival benefit of rituximab maintenance in patients with follicular lymphoma: long-term results of the PRIMA study. *Journal of Clinical Oncology*. 2019 Nov 11;37(31):2815.
- Jurinic V, Kridel R, Staiger AM, Szczepanowski M, Horn H, Dreyling MH, Rosenwald A, Ott G, Klapper W, Zelenetz AD, Barr PM. Clinicogenetic risk models predict early progression of follicular lymphoma after first-line immunochemotherapy. *Blood, The Journal of the American Society of Hematology*. 2016 Aug 25;128(8):1112-20.
- Jacobson CA, Chavez JC, Sehgal AR, William BM, Munoz J, Salles G, Munshi PN, Casulo C, Maloney DG, de Vos S, Reshef R. Axicabtagene ciloleucel in relapsed or refractory indolent non-Hodgkin lymphoma (ZUMA-5): a single-arm, multicentre, phase 2 trial. *The lancet oncology*. 2022 Jan 1;23(1):91-103.
- Fowler NH, Dickinson M, Dreyling M, Martinez-Lopez J, Kolstad A, Butler J, Ghosh M, Popplewell L, Chavez JC, Bachy E, Kato K. Tisagenlecleucel in adult relapsed or refractory follicular lymphoma: the phase 2 ELARA trial. *Nature medicine*. 2022 Feb;28(2):325-32.
- Jacobson CA, Chavez JC, Sehgal A, William BM, Munoz J, Salles GA, Casulo C, Munshi PN, Maloney DG, De Vos S, Reshef R. Outcomes in ZUMA-5 with axicabtagene ciloleucel (axi-cel) in patients (pts) with relapsed/refractory (R/R) indolent non-Hodgkin lymphoma (iNHL) who had the high-risk feature of progression within 24 months from initiation of first anti-CD20-containing chemoimmunotherapy (POD24).
- Thieblemont C, Dickinson M, Martinez-Lopez J, Kolstad A, Butler JP, Ghosh M, Popplewell LL, Chavez JC, Bachy E, Kato K, Harigae H. Efficacy of tisagenlecleucel in adult patients (Pts) with high-risk relapsed/refractory follicular lymphoma (r/r FL): subgroup analysis of the phase II Elara study. *Blood*. 2021 Nov 23;138:131.
- Abramson JS, Palomba ML, Gordon LI, Lunning MA, Wang M, Arnason J, Mehta A, Purey E, Maloney DG, Andreadis C, Sehgal A. Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. *The Lancet*. 2020 Sep 19;396(10254):839-52.
- Budde LE, Bartlett NL. Single-agent mosunetuzumab shows durable complete responses in patients with relapsed or refractory B-cell lymphomas: phase I dose-escalation study. *American Society of Clinical Oncology*.
- Budde LE, Sehn LH, Mataras M, Schuster SJ, Assouline S, Giri P, Kuruvilla J, Canales M, Dietrich S, Fay K, Ku M. Safety and efficacy of mosunetuzumab, a bispecific antibody, in patients with relapsed or refractory follicular lymphoma: a single-arm, multicentre, phase 2 study. *The Lancet Oncology*. 2022 Aug 1;23(8):1055-65.
- Hutchings M, Morschhauser F, Iacoboni G, Carlo-Stella C, Offner FC, Sureda A, Salles G, Martinez-Lopez J, Crump M, Thomas DN, Morcos PN. Glofitamab, a novel, bivalent CD20-targeting T-cell-engaging bispecific antibody, induces durable complete remissions in relapsed or refractory B-cell lymphoma: a phase I trial. *Journal of Clinical Oncology*. 2021 Jun 6;39(18):1959.
- Hutchings M, Mous R, Clausen MR, Johnson P, Linton KM, Chamuleau ME, Lewis DJ, Balari AS, Cunningham D, Oliveri RS, Elliott B. Dose escalation of subcutaneous epcoritamab in patients with relapsed or refractory B-cell non-Hodgkin lymphoma: an open-label, phase 1/2 study. *The Lancet*. 2021 Sep 25;398(10306):1157-69.
- Bannerji R, Arnason JE, Advani RH, Brown JR, Allan JN, Ansell SM, Barnes JA, O'Brien SM, Chavez JC, Duell J, Rosenwald A. Odronektamab, a human CD20× CD3 bispecific antibody in patients with CD20-positive B-cell malignancies (ELM-1): results from the relapsed or refractory non-Hodgkin lymphoma cohort in a single-arm, multicentre, phase 1 trial. *The Lancet Haematology*. 2022 May 1;9(5):e327-39.
- Siddiqi T, Soumerai JD, Dorritie KA, Stephens DM, Riedell PA, Arnason J, Kipps TJ, Gillenwater HH, Gong L, Yang L, Ogasawara K. Phase I TRANSCEND CLL 004 study of lisocabtagene maraleucel in patients with relapsed/refractory CLL or SLL. *Blood*. 2022 Mar 24;139(12):1794-806.
- Turtle CJ, Hay KA, Hanafi LA, Li D, Cherian S, Chen X, Wood B, Lozanski A, Byrd JC, Heimfeld S, Riddell SR. Durable molecular remissions in chronic lymphocytic leukemia treated with CD19-specific chimeric antigen receptor-modified T cells after failure of ibrutinib. *Journal of Clinical Oncology*. 2017 Sep 9;35(26):3010.
- Gauthier J, Hirayama AV, Purushe J, Hay KA, Lymp J, Li DH, Yeung CC, Sheih A, Pender BS, Hawkins RM, Vakil A. Feasibility and efficacy of CD19-targeted CAR T cells with concurrent ibrutinib for CLL after ibrutinib failure. *Blood, The Journal of the American Society of Hematology*. 2020 May 7;135(19):1650-60.
- Porter DL, Hwang WT, Frey NV, Lacey SF, Shaw PA, Loren AW, Bagg A, Marcucci KT, Shen A, Gonzalez V, Ambrose D. Chimeric antigen receptor T cells persist and induce sustained remissions in relapsed refractory chronic lymphocytic leukemia. *Science translational medicine*. 2015 Sep 2;7(303):303ra139.
- Kater AP, Christensen JH, Bentzen HH, Niemann CU, Hutchings M, Chen J, Rios M, Palenski T, Li T, Mato AR. Subcutaneous epcoritamab in patients with relapsed/refractory chronic lymphocytic leukemia: preliminary results from the Epcore CLL-1 trial. *Blood*. 2021 Nov 23;138:2627.

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EVOLVING ROLE OF NOVEL THERAPIES IN MYELOMA: T-CELL ENGAGERS AND ANTIBODY DRUG CONJUGATES

Introduction

Multiple myeloma (MM) is a hematologic malignancy characterized by the proliferation of abnormal clonal plasma cells. This population of neoplastic plasma cells can subsequently cause damaging lytic lesions to the bones, kidney dysfunction, high levels of calcium in the blood, and anemia.¹ MM is more prevalent in individuals over age 65 than in younger individuals; the median age at diagnosis is 69 years old. This malignancy is generally considered incurable. The five-year overall survival (OS) is estimated to be as high as 82% with the Revised International Staging System (R-ISS) for Stage I of the disease, and 40% with R-ISS Stage III of the disease.² A large proportion of patients in the relapsed/refractory (R/R) setting are unable to achieve durable responses to treatment. There remains an unmet need for novel, highly effective and well-tolerated therapies in this patient population.³

Treatment of myeloma patients has evolved in the past two decades with the introduction of novel therapies:⁴ the proteasome inhibitors (PIs) bortezomib, carfilzomib and ixazomib; the immunomodulatory imide drugs (IMiDs) thalidomide, lenalidomide and pomalidomide; and the anti-CD38 monoclonal antibodies (MoAb's) daratumumab and isatuximab. All of these therapeutic agents have demonstrated improved outcomes in myeloma patients.^{3,5} Survival of myeloma patients continues to improve over time, particularly with the combination of novel first-line and subsequent agents, resulting in median OS of 8 to 12 years.⁶ Survival data in Canada is very similar with median OS of >10 years.⁷

Outcomes of patients with R/R myeloma continues to be an additional important area of unmet need. Clinical data have reported poor outcomes for patients who have become refractory to PIs, IMiDs and MoAb's, with progression-free survival (PFS) of 3.4 months and OS of 9.3 months.⁸ This has been confirmed, as well, by real-world data from Canadian patients, with reported PFS of 4.4 months and OS of 10.5 months in triple-class refractory patients.⁹

BCMA as a Therapeutic Target

B-cell maturation antigen (BCMA) is a cell surface protein expressed on late-stage B-cells and plasma cells. It is virtually absent on naïve and memory cells and highly expressed on malignant plasma cells in all patients with myeloma. It is essential for the proliferation and survival of malignant plasma cells.¹⁰⁻¹² In myeloma, BCMA has been targeted as a major area of T-cell engager and antibody-drug conjugate (ADC) research.^{12,13}

T-cell Engagers

T-cell engagers are unique constructs that simultaneously bind two antigens, usually engaging an antigen on the tumor and a molecule on an immune cell; this results in immune cell activation and tumor lysis. T-cell engagers teclistamab and elranatamab (both of which target BCMA) recently received FDA approval for use in relapsed myeloma with at least three prior lines of therapy.

Teclistamab is a T-cell engager (BCMAxCD3). The Phase 1-2 Majes TEC-1 clinical study involved 165 patients with

relapsed myeloma with at least 3 prior lines of therapy, and prior use of PI/IMiD and anti-CD38 antibody therapy. At baseline, 77.6% of the subjects were triple-class refractory and had a median of five prior lines of therapy. They demonstrated a 63% OR (39.4% complete response [CR]), with a median PFS of 11.3 months. Cytokine release syndrome (CRS) was present in 72.1% of patients, the majority of which were Grade 1/2; cytopenias (70.9% neutropenia) and infections (76.4%) were common, and 14.5% of patients had some grade of neurological toxicity.¹⁴

Elranatamab is a bispecific T-cell engager. MagnetisMM-3 was a Phase 2 clinical trial involving 123 relapsed myeloma patients who had received at least 3 prior lines of therapy, all of whom were refractory to a PI, an IMiD and anti-CD38 antibody. They had all received a median of five prior lines of therapy; the overall response rate (ORR) was 61%; the median PFS had not been reached; CRS was 57.7%; anemia occurred in 45.5% of patients; neutropenia occurred in 43.1% of patients; infections were common and were reported in 61.8% of patients; and neurological toxicity was reported in 3.4% of patients.¹⁵

Target	Product	n	ORR	CR
BCMA	Teclistamab	165	63%	39.40%
BCMA	Elranatamab	123	61%	NA
BCMA	CC-93269	30	43%	17%
BCMA	AMG-701	85	26%	10%
BCMA	REGN5458	49	39%	16%
BCMA	TNB-383B	58	47%	14%

Table 1 T-cell engagers currently being studied¹³

Additional BCMA T-cell engager agents (engaging BCMAxCD3) for the treatment of R/R myeloma are currently under investigation (**Table 1**).

Aside from BCMA, other antigen targets under investigation for T-cell engagers in R/R myeloma include FcRH5 and GPRC5D, both of which have demonstrated initial results that are encouraging.

Cevostamab, a FcRH5xCD3 construct, was investigated in a Phase I trial involving 160 patients with myeloma who had received a median of six prior lines of therapy. The study results demonstrated an ORR ranging from 53% to 61% at higher doses, with manageable CRS.¹⁶ Long-term data suggest that patients can maintain durable therapeutic response.¹⁷

Talquetamab, a GPRC5DxCD3 construct, was investigated in MonumentAL-1, a Phase 1-2 trial involving 288 patients who had received a median of five prior lines of therapy,

with two different dosing regimens of 0.4 mg/kg weekly or 0.8 mg/kg q2 weeks. The study results reported an ORR of 74.1 to 73.1%, with median PFS of 7.5 to 11.9 months. CRS was 72.1% to 79%, primarily Grade 1/2. Adverse events were common and the following were observed with the 0.4 mg/kg QW dosing regimen: Anemia occurred in 44.8% of patients; neutropenia occurred in 34.3% of patients; Infections were common (57.3%); skin-related AEs (55.9%); and nail disorders (51.7%). Rash occurred in 39.2% of patients; dysgeusia occurred in 48.3% of patients. Neurological toxicity was reported at 10.7%. All of these adverse events were managed with supportive care.¹⁸

A pooled analysis of 11 studies involving 1,185 patients treated with bispecific T cell engager, 71.6% of them targeting BCMA, showed that those targeting BCMA resulted in 34.8% grade 3/4 neutropenia, and 24.5% grade 3/4 infections including 10% grade 3/4 pneumonia and 11.4% grade 3/4 COVID-19 infections. Non-BCMA bispecific T cell engager were associated with lower risk for neutropenia and infections. This pooled analysis also showed a prevalence of 75.3% of hypogammaglobulinemia. Typical and opportunistic infections including cytomegalovirus, candida, herpes virus, pneumocystis were reported with the use of these agents.¹⁹

Antibody Drug Conjugates

ADCs are MoAb's that contain a cytotoxic drug linked as a payload that releases upon internalization on the antibody. Combinations of a MoAB and a cytotoxic drug are not new. This strategy has been used previously to treat Hodgkin's lymphoma (brentuximab vedotin); and in acute myeloid leukemia (gemtuzumab ozogamicin). Several ADCs have been studied in relapsed myeloma, in most cases as an antibody targeting BCMA, with various cytotoxic drugs used as payloads (**Table 2**).¹³

Belantamab mafodotin is a humanized afucosylated, IgG1 BCMA-targeted ADC that neutralizes soluble BCMA, with monomethyl auristatin F (MMAF) as its cytotoxic payload. It has four mechanisms of action: antibody-dependent cellular cytotoxicity, immunogenic cell death, BCMA receptor signaling inhibition, and ADC. It was approved in August of 2020 for patients with R/R myeloma who have received >4 lines of therapy including a PI, an IMiD and an anti-CD38 antibody.^{12,20,21}

The Phase 1 DREAMM-1 trial involving 35 patients with refractory myeloma showed an ORR of 60%.²² Phase 2 data from the DREAMM-2 trial involving 196 patients comparing two doses, 2.5mg/kg q3 week and 3.4 mg/kg q3 week, reported an ORR of 30-34% with a median PFS of 2.9 to 4.9 months.²³ The Phase 3 DREAMM-3 trial involving 325 patients, comparing belantamab mafodotin 2.5 mg/kg q3 week to pomalidomide plus dexamethasone in R/R myeloma

Name	Target	Cytotoxic agent	Combination	Phase (number of patients)	Response
Belantamab mafodotin	BCMA	MMAF	Monotherapy	1; n=35	ORR 60%
			Monotherapy	2; n=96	ORR 30-34%
			B vs Pd	3; n=325	ORR 41%
			B-Pd	1/2; n=96	ORR 88.9%
			B-Pd vs V-Pd	3; n=450	N/A
MEDI2228	BCMA	PBD	Monotherapy	1; n=82	ORR 66%
CC 99712	BCMA	Maytansinoid-like	Monotherapy	1; n=160	N/A
AMG 224	BCMA	Mertansine	Monotherapy	1; n=42	ORR 27%

Table 2. ADCs currently being studied in relapsed myeloma¹³

did not meet its primary endpoint of PFS (11.2 vs 7 months; HR 1.03; 95% CI, 0.72-1.47). It reported an ORR of 41% vs 36%.^{24,25}

Common adverse events with belantamab mafodotin include keratopathy, thrombocytopenia, and anemia. Corneal toxicity was associated with the MMAF cytotoxic payload; most ocular toxicity was reversible when holding treatment. In certain subsequent trials of combination therapy, the incidence of keratopathy was as high as 81%.^{23,24}

MEDI2228 is a fully humanized anti-BCMA antibody conjugated with pyrrollobenzodiazepine (a DNA cross-linking agent), which binds to membrane bound BCMA. A Phase 1 dose finding and toxicity study is ongoing.²⁶

Conclusion

In the past 20 years, the advent of novel agents for the treatment of MM has definitely led to a notable improvement in survival, from 3-4 years in the 1990s to close to 8-12 years, according to the most recent data.^{6,7}

Immunotherapies such as T-cell engagers and ADC-targeting novel antigens such as BCMA in myeloma are promising therapeutic options. Early clinical trial results show median PFS (11.3 months) that is significantly greater than that of standard of care options for heavily pretreated R/R myeloma (4.4 months).⁹

The advantage of ADCs and T-cell engagers is that they are readily available compared to that of other novel approaches such as CAR T-cell therapy which may require a lengthy manufacturing process and may result in delays in some cases due to supply chain issues. However, these agents also have disadvantages such as the need for ongoing treatment, especially when compared to a single dose of CAR T-cell therapy. Furthermore, in some cases, these novel agents are associated with new toxicities, such as ocular toxicity (keratopathy) which may limit their use or lead to dosing delays.

The future for myeloma patients appears promising, with a growing number of therapeutic options. These include non-BCMA antigen targeted therapy and CAR T-cell therapy, which have shown anti-myeloma activity in R/R myeloma, and the use of more active triplet and quadruplet regimens in a first-line setting.

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References:

- Dimopoulos MA, Jakubowiak AJ, McCarthy PL, Orlowski RZ, Attal M, Bladé J, Goldschmidt H, Weisel KC, Ramasamy K, Zweegman S, Spencer A. Developments in continuous therapy and maintenance treatment approaches for patients with newly diagnosed multiple myeloma. *Blood Cancer Journal*. 2020 Feb 13;10(2):17.
- Palumbo A, Avet-Loiseau H, Oliva S, Lokhorst HM, Goldschmidt H, Rosinol L, Richardson P, Caltagirone S, Lahuerta JJ, Facon T, Brinchen S. Revised international staging system for multiple myeloma: a report from International Myeloma Working Group. *Journal of Clinical Oncology*. 2015 Sep 9;33(26):2863.
- Bhatt P, Kloock C, Comenzo R. Relapsed/Refractory Multiple Myeloma: A Review of Available Therapies and Clinical Scenarios Encountered in Myeloma Relapse. *Current Oncology*. 2023 Feb 15;30(2):2322-47.
- Kumar SK, Rajkumar SV, Dispenzieri A, Lacy MQ, Hayman SR, Buadi FK, Zeldenrust SR, Dingli D, Russell SJ, Lust JA, Greipp PR. Improved survival in multiple myeloma and the impact of novel therapies. *Blood, The Journal of the American Society of Hematology*. 2008 Mar 1;111(5):2516-20.
- Gonsalves WI, Milani P, Derudas D, Buadi FK. The next generation of novel therapies for the management of relapsed multiple myeloma. *Future Oncology*. 2017 Jan;13(1):63-75.
- Puertas B, González-Calle V, Sobejano-Fuertes E, Escalante F, Queizán JA, Báez A, Labrador J, Alonso-Alonso JM, García de Coca A, Cantalapiedra A, Villaseca T. Novel Agents as Main Drivers for Continued Improvement in Survival in Multiple Myeloma. *Cancers*. 2023 Mar 2;15(5):1558.
- Cote J, Leblanc R, Chu MP, McCurdy A, Masih-Khan E, Kardjadj M, Jimenez-Zepeda VH, Song K, Louzada ML, Mian HS, White D. Real-World Results of Autologous Stem Cell Transplantation in Newly Diagnosed Patients with Multiple Myeloma: A Multi-Institutional Report from the Canadian Myeloma Research Group (CMRG) Database. *Blood*. 2022 Nov 15;140(Supplement 1):289-91.
- Gandhi UH, Cornell RF, Lakshman A, Gahvari ZJ, McGehee E, Jagosky MH, Gupta R, Varnado W, Fiala MA, Chhabra S, Malek E. Outcomes of patients with multiple myeloma refractory to CD38-targeted monoclonal antibody therapy. *Leukemia*. 2019 Sep;33(9):2266-75.
- Visram A, De La Torre A, White D, Kardjadj M, Masih-Khan E, Chu MP, Jimenez-Zepeda VH, McCurdy A, Leblanc R, Song K, Mian HS. Real World Data on Outcomes of Anti-CD38 Antibody Refractory, Including Triple Class Refractory, Patients with Multiple Myeloma: A Multi-Institutional Report from the Canadian Myeloma Research Group (CMRG) Database. *Blood*. 2022 Nov 15;140(Supplement 1):4287-9.
- Tai YT, Anderson KC. Targeting B-cell maturation antigen in multiple myeloma. *Immunotherapy*. 2015 Nov;7(11):1187-99.
- Cho SF, Anderson KC, Tai YT. Targeting B cell maturation antigen (BCMA) in multiple myeloma: potential uses of BCMA-based immunotherapy. *Frontiers in immunology*. 2018 Aug 10;9:1821.
- Tai YT, Mayes PA, Acharya C, Zhong MY, Cea M, Cagnetta A, Craig J, Yates J, Gliddon L, Fieles W, Hoang B. Novel anti-B-cell maturation antigen antibody-drug conjugate (GSK2857916) selectively induces killing of multiple myeloma. *Blood, The Journal of the American Society of Hematology*. 2014 May 15;123(20):3128-38.
- Cipkar C, Chen C, Trudel S. Antibodies and bispecifics for multiple myeloma: effective effector therapy. *Hematology*. 2022 Dec 9;2022(1):163-72.
- Moreau P, Garfall AL, van de Donk NW, Nahi H, San-Miguel JF, Oriol A, Nooka AK, Martin T, Rosinol L, Chari A, Karlin L. Teclistamab in relapsed or refractory multiple myeloma. *New England Journal of Medicine*. 2022 Aug 11;387(6):495-505.
- Bahlis NJ, Tomasson MH, Mohty M, Niesvizky R, Nooka AK, Manier S, Maisel C, Jethava Y, Martinez-Lopez J, Prince HM, Arnulf B. Efficacy and Safety of Elranatamab in Patients with Relapsed/Refractory Multiple Myeloma Naïve to B-Cell Maturation Antigen (BCMA)-Directed Therapies: Results from Cohort a of the MagnetisMM-3 Study. *Blood*. 2022 Nov 15;140(Supplement 1):391-3.
- Trudel S, Cohen AD, Krishnan AY, Fonseca R, Spencer A, Berdeja JG, Lesokhin A, Forsberg PA, Laubach JP, Costa LJ, Rodriguez-Otero P. Cevostamab monotherapy continues to show clinically meaningful activity and manageable safety in patients with heavily pre-treated relapsed/refractory multiple myeloma (RRMM): updated results from an ongoing phase I study. *Blood*. 2021 Nov 23;138:157.
- Lesokhin AM, Richter J, Trudel S, Cohen AD, Spencer A, Forsberg PA, Laubach JP, Thomas SK, Bahlis NJ, Costa LJ, Rodriguez Otero P. Enduring Responses after 1-Year, Fixed-Duration Cevostamab Therapy in Patients with Relapsed/Refractory Multiple Myeloma: Early Experience from a Phase I Study. *Blood*. 2022 Nov 15;140(Supplement 1):4415-7.
- Chari A, Touzeau C, Schinke C, Minnema MC, Berdeja J, Oriol A, Van De Donk NW, Rodriguez Otero P, Askari E, Mateos MV, Costa LJ. Talquetamab, a G Protein-Coupled Receptor Family C Group 5 Member D x CD3 Bispecific Antibody, in Patients with Relapsed/Refractory Multiple Myeloma (RRMM): Phase 1/2 Results from MonumenTAL-1. *Blood*. 2022 Nov 15;140(Supplement 1):384-7.
- Mazahreh F, Mazahreh L, Schinke C, Thanendrarajan S, Zangari M, Shaughnessy JD, Zhan F, Van Rhee F, Al Hadidi SA. Risk of infections associated with the use of bispecific antibodies in multiple myeloma: a pooled analysis. *Blood Adv*. 2023 Mar 1;bloodadvances.2022009435. doi: 10.1182/bloodadvances.2022009435. Epub ahead of print. PMID: 36857755.
- Trudel S, Lendvai N, Popat R, Voorhees PM, Reeves B, Libby EN, Richardson PG, Anderson LD, Sutherland HJ, Yong K, Hoos A. Targeting B-cell maturation antigen with GSK2857916 antibody-drug conjugate in relapsed or refractory multiple myeloma (BMA117159): a dose escalation and expansion phase 1 trial. *The Lancet Oncology*. 2018 Dec 1;19(12):1641-53.
- Markham A. Belantamab Mafodotin: First Approval. *Drugs*. 2020 Oct;80(15):1607-1613.
- Trudel S, Lendvai N, Popat R, Voorhees PM, Reeves B, Libby EN, Richardson PG, Hoos A, Gupta I, Bragulat V, He Z. Antibody-drug conjugate, GSK2857916, in relapsed/refractory multiple myeloma: an update on safety and efficacy from dose expansion phase I study. *Blood Cancer Journal*. 2019 Mar 20;9(4):1-0.
- Lonial S, Lee HC, Badros A, Trudel S, Nooka AK, Chari A, Abdallah AO, Callander N, Lendvai N, Sborov D, Suvannasankha A. Belantamab mafodotin for relapsed or refractory multiple myeloma (DREAMM-2): a two-arm, randomised, open-label, phase 2 study. *The Lancet Oncology*. 2020 Feb 1;21(2):207-21.
- Weisel K, Hopkins TG, Fecteau D, Bao W, Quigley C, Jewell RC, Nichols M, Opalinska J. Dreamm-3: a phase 3, open-label, randomized study to evaluate the efficacy and safety of belantamab mafodotin (GSK2857916) monotherapy compared with pomalidomide plus low-dose dexamethasone (Pom/Dex) in participants with relapsed/refractory multiple myeloma (RRMM). *Blood*. 2019 Nov 13;134:1900.
- GSK provides update on DREAMM-3 phase III trial for Blenrep in relapsed/refractory multiple myeloma. News release. GSK. November 7, 2022. Accessed November 8, 2022. <https://bit.ly/3FYNEB>.
- Tai YT, Xing L, Lin L, Yu T, Cho SF, Wen K, Kinneer K, Munshi N, Anderson KC. MEDI2228, a novel BCMA pyrrolizidinecarboxamide antibody drug conjugate, overcomes drug resistance and synergizes with bortezomib and DNA damage response inhibitors in multiple myeloma. *Clinical Lymphoma, Myeloma and Leukemia*. 2019 Oct 1;19(10):e154-5.

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ACUTE MYELOID LEUKEMIA INDUCTION IN THE AGE OF NOVEL THERAPEUTIC AGENTS

Introduction

Acute myeloid leukemia (AML) is a malignant neoplasm of the myeloid lineage characterized by the uncontrolled proliferation of immature myeloid blasts in the bone marrow and peripheral blood. AML is a heterogeneous disease which occurs across the age spectrum, although with an increasing incidence with age. For decades, first-line, curative-intent therapy has been based on intensive therapy with anthracycline (typically daunorubicin or idarubicin) plus cytarabine (3+7), followed by additional consolidative chemotherapy and/or allogeneic stem cell transplantation. While improvements over the decades in overall survival have been observed, until recently this has been driven largely by advancements in supportive care leading to reduction in treatment-related mortality and allowing a greater proportion of patients (particularly older individuals) to safely undergo intensive therapy induction and consolidation. Despite this, five-year overall survival (OS) rates in older individuals are as low as 5% (age >70). Although OS for patients age 15-39 is now in the range of 50%-60%, a large portion of patients still succumb to their disease. Cytogenetic and molecular profiling has led to defined risk categories (**Table 1**), and complete risk stratification for all patients eligible for intensive therapy is

crucial to aiding in the selection of optimal induction and post-remission therapy. In recent years, an improved understanding of AML biology and genetics has led to the approval of a number of novel therapies for patients deemed fit and unfit for intensive therapy, which may finally be moving the needle beyond 3+7. This article will review a current approach to AML induction patients eligible for intensive therapy, with a focus on the utilization of available novel agents.

FLT3 Inhibition

FLT3 is a receptor tyrosine kinase that plays a crucial role in the pathogenesis of AML. Aberrations in FLT3 are present in approximately 30% of AML cases, with internal tandem duplication (ITD) generally associated with a poor prognosis in the majority of cases, and with tyrosine kinase domain (TKD) mutations having less certain impact on outcome. FLT3 has therefore become an attractive therapeutic target, and FLT3 tyrosine kinase inhibitors (TKIs) have emerged as adjuncts to AML induction, and as monotherapy for relapsed disease. Midostaurin is a multi-kinase inhibitor that targets FLT3, as well as other kinases involved in AML pathogenesis (including Src kinase, spleen tyrosine kinase, c-kit). The Phase 3 RATIFY trial randomized patients age 18 to 59 with newly

diagnosed AML and FLT3 mutations (either ITD or TKD) to receive standard induction therapy with daunorubicin and cytarabine and high- dose cytarabine consolidation, plus either placebo or midostaurin. The complete remission (CR) rate was improved by the addition of midostaurin (59% vs 54%), with a median OS of 74.7 months in the midostaurin arm and 25.6 months in the control arm. This survival benefit was seen in cohorts with both high- and low-FLT3 allelic burden. In the Phase 3 ADMIRAL clinical trial, gilteritinib, a more selective FLT3 inhibitor, was demonstrated to have superior efficacy vs salvage chemotherapy in patients with relapsed or refractory FLT3-mutated AML. CR or CR with incomplete hematologic recovery was reported as 34% in the gilteritinib arm and 15.3% in the chemotherapy cohort, with median event-free survival of 2.3 months versus 0.3 months. A clinical study comparing the addition of gilteritinib versus the addition of midostaurin to induction and consolidation is ongoing. Midostaurin is Health Canada approved in combination with standard induction and consolidation for newly diagnosed FLT3-mutated AML; gilteritinib is approved as monotherapy for patients with relapsed or refractory FLT3-mutated disease.

Gemtuzumab ozogamicin

Gemtuzumab ozogamicin (GO) is an anti-CD33 monoclonal antibody conjugated to calicheamicin with previous approval for relapsed/refractory (RR) AML. FDA approval was withdrawn in 2010 due to safety concerns (largely related to an increased risk of sinusoidal occlusive syndrome). However, it was reapproved by the FDA in 2017, and is Health Canada approved in combination with 3+7 for previously untreated CD33-positive AML (excluding acute promyelocytic leukemia [APL]). The ALFA-0701 clinical trial randomized patients to receive GO on Days 1, 4 and 7 of induction, as well as up to two consolidation cycles. The addition of GO did not appear to increase rates of CR (73% with GO vs 72% without GO), but resulted in a significant improvement in 2-year event-free survival (41% vs 7%). Although the ALFA-0701 trial did not show a statistically significant OS benefit with the addition of GO, a subsequent meta-analysis of five trials suggests that the addition of GO to standard therapy does provide an OS benefit for patients with favourable and intermediate risk CD33-positive AML, but not for adverse risk patients. In particular, for patients with core binding factor (CBF) AML, the addition of GO results in improved minimal residual disease (MRD) clearance, and may reduce the need for subsequent allogeneic stem cell transplant in this population.

IDH1 and IDH2 Inhibitors

Isocitrate dehydrogenase (IDH) mutations occur in approximately 20% of AML cases and are associated with an adverse prognosis. Inhibitors of IDH1 (ivosidenib) and IDH2 (enasidenib) have been developed. Both agents have monotherapy activity in RR IDH-mutated AML,^{10,11} and the

addition of ivosidenib to azacitidine resulted in improved response rates and EFS in newly diagnosed IDH1-mutated AML not eligible for intensive therapy. The ongoing HOVON study is evaluating the addition of ivosidenib and enasidenib to induction/consolidation and as maintenance in patients with IDH1/IDH2-mutated AML eligible for intensive therapy. Both agents are Health Canada approved for RR IDH1 and IDH2 mutated AML, respectively, although lack of provincial funding may provide barriers to their access.

Venetoclax

B-cell lymphoma-2 (BCL-2) is an anti-apoptotic protein which plays an important role in a number of hematologic malignancies, including AML. Venetoclax, a BCL-2 inhibitor, has been shown to improve OS when added to azacitidine (median OS 14.7 months vs 9.6 months) and low- dose cytarabine (in longer term follow-up, it has shown median OS of 7.2 months vs 4.1 months) in patients with newly diagnosed AML ineligible for intensive therapy (VIALE-A and VIALE-C trials, respectively). Both combinations are Health Canada approved. Venetoclax, in addition to 3+7 induction, resulted in high CR rates (91%, with 97% of patients achieving CR being MRD-negative) in a Phase II study, and an ongoing Phase 3 study is evaluating this combination in AML and advanced myelodysplastic syndromes (MDS).

Liposomal encapsulated daunorubicin and cytarabine

While “therapy-related” AMLs are now defined more by their predisposition for high-risk genetic profiles than by history of previous treatment exposure alone, the fact remains that the majority harbour adverse risk genetic abnormalities, and these leukemias are typically associated with a poor outcome. Likewise, AML arising from antecedent myelodysplasia or myeloproliferative neoplasms (MPNs) is also typically associated with adverse outcomes. The combination of liposomal encapsulated cytarabine and daunorubicin (CPX-351) was evaluated in older patients (age 60-75 years) with newly diagnosed high-risk secondary AML (defined in this trial as therapy-related AML, AML with antecedent MDS or chronic myelomonocytic leukemia (CMML), or AML with MDS-related cytogenetic abnormalities). Patients were randomly assigned to receive standard 3+7 induction and cytarabine consolidation, or up to two induction cycles and two consolidation cycles of the liposomal combination. Higher overall response rates (ORRs) were observed with CPX-351 vs standard therapy (ORR 47.7% vs 33.3%), and there was an OS benefit in the study arm (median OS 9.56 vs 5.95 months). Of note, patients who had received prior hypomethylating therapy did not appear to benefit in subgroup analysis, and patients with antecedent MPNs including primary myelofibrosis, essential thrombocytosis, polycythemia vera, and MDS-MPN overlap were excluded from the trial. Retrospective data presents conflicting evidence of benefit for younger patients treated with CPX-351, and further clinical studies are required to

Risk Category	Genetic Abnormalities
Favourable	t(8;21)(q22;q22.1)/ <i>RUNX1::RUNX1T1</i> inv(16)(p13.1;q22) or t(16;16)(p13.1;q22)/ <i>CBFB::MYH11</i> Mutated <i>NPM1</i> without <i>FLT3</i> -ITD bZIP in-frame mutated <i>CEBPA</i>
Intermediate	Mutated <i>NPM1</i> with <i>FLT3</i> -ITD Wild-type <i>NPM1</i> with <i>FLT3</i> -ITD t(9;11)(p21.3;q23.3)/ <i>MLLT3::KMT2A</i> Cytogenetic and/or molecular abnormalities not classified as favourable or adverse
Adverse	t(6;9)(p23;q34.1)/ <i>DEK::NUP214</i> t(v;11q23.3)/ <i>KMT2A</i> -rearranged t(9;22)(q34.1;q11.2)/ <i>BCR::ABL1</i> t(8;16)(p11;p13)/ <i>KAT6A::CREBBP</i> inv(3)(q21.3;q26.2) or t(3;3)(q21.3;q26.2)/ <i>GATA2, MECOM(EV11)</i> t(3q26.2;v)/ <i>MECOM(EV11)</i> -rearranged -5 or del(5q); -7; -17/abn(17p) Complex karyotype, monosomal karyotype Mutated <i>ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, or ZRSR2</i> Mutated <i>TP53</i>

Table 1. European Leukemia Net 2022 AML Risk Stratification Schema²¹

define its optimal role in this patient population., CPX-351 is Health Canada approved for the treatment of adults with newly diagnosed therapy-related AML or AML with MDS-related changes.

Oral azacitidine

Patients with AML successfully completing intensive induction therapy require additional post-remission consolidation, either with additional chemotherapy (favourable risk disease) or allogeneic stem cell transplantation (most non-favourable risk disease). Review of patient selection for and outcomes of allogeneic stem cell transplantation is beyond the scope of this article; however, patients with non-favourable risk disease who are unable to proceed with allogeneic stem cell transplant typically have poor outcomes. The QUAZAR AML-001 randomized, placebo-controlled clinical trial reported that in AML patients in remission following intensive chemotherapy but unable to proceed to hematopoietic stem cell transplant, oral azacitidine maintenance therapy (administered Day 1-14/28 day cycles) improved median OS (24.7 months vs 14.8 months), as well as relapse-free survival. These results were evident in patients who did not receive any additional consolidative therapy post-induction. Oral azacitidine is Health Canada approved for maintenance therapy in adult patients with AML who achieved CR or complete remission with incomplete count recovery (CRi) following induction therapy who are not eligible for hematopoietic stem cell transplant.

Conclusion

After an extended period of limited progress in AML induction therapy, recent advances have led to the approval

of a number of novel agents for the treatment of AML in both fit and less fit patients, leading to improved outcomes for many of these patients. The optimal utilization of many of these agents remains to be defined, but prompt and complete molecular characterization of patients with newly diagnosed AML is more crucial than ever to ensure access to the most effective therapies. While novel agents have improved RRs and survival, many patients are still not cured of their disease. Numerous novel therapies, including small-molecule inhibitors (SMIs), immunotherapies and cellular therapies, are currently under investigation and offer hope for further improvements in long-term outcomes in the future.

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References:

1. Sasaki K, Ravandi F, Kadia TM, DiNardo CD, Short NJ, Borthakur G, Jabbour E, Kantarjian HM. De novo acute myeloid leukemia: A population-based study of outcome in the United States based on the Surveillance, Epidemiology, and End Results (SEER) database, 1980 to 2017. *Cancer*. 2021 Jun 15;127(12):2049-61.
2. Fröhling S, Schlenk RF, Breitruck J, Benner A, Kreitmeier S, Tobis K, Döhner H, Döhner K. Prognostic significance of activating FLT3 mutations in younger adults (16 to 60 years) with acute myeloid leukemia and normal cytogenetics: a study of the AML Study Group Ulm. *Blood, The Journal of the American Society of Hematology*. 2002 Dec 15;100(13):4372-80.
3. Abbas HA, Alfayez M, Kadia T, Ravandi-Kashani F, Dayer N. Midostaurin in acute myeloid leukemia: an evidence-based review and patient selection. *Cancer Management and Research*. 2019;11:8817.
4. Stone RM, Mandrekas SJ, Sanford BL, Laumann K, Geyer S, Bloomfield CD, Thiede C, Prior TW, Döhner K, Marcucci G, Lo-Coco F. Midostaurin plus chemotherapy for acute myeloid leukemia with a FLT3 mutation. *New England Journal of Medicine*. 2017 Aug 3;377(5):454-64.
5. Perl AE, Martinelli G, Cortes JE, Neubauer A, Berman E, Paolini S, Montesinos P, Baer MR, Larson RA, Ustun C, Fabbiano F. Gilteritinib or chemotherapy for relapsed or refractory FLT3-mutated AML. *New England Journal of Medicine*. 2019 Oct 30;381:1728-1740.
6. Gilteritinib vs Midostaurin in FLT3 Mutated AML. *ClinicalTrials.gov*. NCT03836209.
7. Castaigne S, Pautas C, Terré C, Raffoux E, Bordessoule D, Bastie JN, Legrand O, Thomas X, Turlure P, Reman O, de Revel T. Effect of gemtuzumab ozogamicin on survival of adult patients with de-novo acute myeloid leukaemia (ALFA-0701): a randomised, open-label, phase 3 study. *The Lancet*. 2012 Apr 21;379(9825):1508-16.
8. Hills RK, Castaigne S, Appelbaum FR, Delaunay J, Petersdorf S, Othus M, Estey EH, Dombret H, Chevret S, Ifrah N, Cahn JY. Addition of gemtuzumab ozogamicin to induction chemotherapy in adult patients with acute myeloid leukaemia: a meta-analysis of individual patient data from randomised controlled trials. *The Lancet Oncology*. 2014 Aug 1;15(9):986-96.
9. Borthakur G, Kantarjian H. Core binding factor acute myelogenous leukemia-2021 treatment algorithm. *Blood Cancer Journal*. 2021;11:114.
10. Montesinos P, Recher C, Vives S, Zarzycka E, Wang J, Bertani G, Heuser M, Calado RT, Schuh AC, Yeh SP, Daigle SR. Ivosidenib and azacitidine in IDH1-mutated acute myeloid leukemia. *New England Journal of Medicine*. 2022 Apr;286(6):1519-31.
11. A Study of Ivosidenib or Enasidenib in Combination with Induction Therapy and Consolidation Therapy, Followed by Maintenance Therapy in Patients with Newly Diagnosed Acute Myeloid Leukemia or Myelodysplastic Syndrome EB2, With an IDH1 or IDH2 Mutation, Respectively, Eligible for Intensive Chemotherapy (HOVON150AML) *ClinicalTrials.gov* NCT03839771.
12. DiNardo CD, Jonas BA, Pullarkat V, Thirman MJ, Garcia JS, Wei AH, Konopleva M, Döhner H, Letai A, Fenaux P, Kolter E. Azacitidine and venetoclax in previously untreated acute myeloid leukemia. *New England Journal of Medicine*. 2020 Aug 13;383(7):617-29.
13. Wei AH, Montesinos P, Ivanov V, DiNardo CD, Novak J, Laribi K, Kim I, Stevens DA, Fiedler W, Pagoni M, Samoilova O. Venetoclax plus LDAC for newly diagnosed AML ineligible for intensive chemotherapy: a phase 3 randomized placebo-controlled trial. *Blood*. 2020 Jun 11;135(24):2137-45.
14. Wang H, Mao L, Qian P, et al. Venetoclax plus 3+7 daunorubicin and cytarabine chemotherapy as first-line treatment for adults with acute myeloid leukemia: a multicentre, single-arm phase 2 trial. *Lancet Hematol* 2022;9:E415-424.
15. Venetoclax Plus Intensive Chemotherapy in AML and Advanced MDS. *ClinicalTrials.gov* NCT05342584
16. OK CY, Patel KP, Garcia-Manero G, et al. Mutational profiling of therapy-related myelodysplastic syndromes and acute myeloid leukemia by next-generation sequencing, a comparison with de novo diseases. *Leukemia Research*. 2015 Mar 1;39:348-54.
17. Lancet JE, Uy GL, Cortes JE, Newell LF, Lin TL, Ritchie EK, Stuart RK, Strickland SA, Hogge D, Solomon SR, Stone RM. CPX-351 (cytarabine and daunorubicin) liposome for injection versus conventional cytarabine plus daunorubicin in older patients with newly diagnosed secondary acute myeloid leukemia. *Journal of Clinical Oncology*. 2018 Sep 9;36(26):2684.
18. Lee D, Jain AG, Deutsch Y, Eatrudes J, Chan O, Padron E, Kuykendall A, Komrokji R, Lancet J, Sallman D, Talati C. CPX-351 yields similar response and survival outcome in younger and older patients with secondary AML. *Clinical Lymphoma, Myeloma and Leukemia*. 2022 Oct 1;22(10):774-9.
19. Przepolewski AC, Talati C, Fazal S, Vachhani P, Sanikomm S, Thota S, Baron J, Griffiths EA, Thompson JE, Sweet KL, Wang ES. Safety and efficacy of CPX-351 in younger patients < 60 years old with secondary acute myeloid leukemia: An updated analysis. *Blood* 2022;138(suppl 1):1264.
20. Wei AH, Döhner H, Pocock C, Montesinos P, Afanasyev B, Dombret H, Ravandi F, Sayar H, Jang JH, Porkka K, Selleslag D. Oral azacitidine maintenance therapy for acute myeloid leukemia in first remission. *New England Journal of Medicine*. 2020 Dec 24;383(26):2526-37.
21. Döhner H, Wei AH, Appelbaum FR, Craddock C, DiNardo CD, Dombret H, Ebert BL, Fenaux P, Godley LA, Hassarjian RP, Larson RA. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. *Blood, The Journal of the American Society of Hematology*. 2022 Sep 22;140(12):1345-77.

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INITIATING VENETOCLAX TREATMENT: CLINICAL PRACTICE PEARLS

Introduction

Overexpression of BCL-2 has been demonstrated in chronic lymphocytic leukemia (CLL) and acute myeloid leukemia (AML) cells where it mediates tumor cell survival and has been associated with resistance to chemotherapeutics. Venetoclax is a selective and orally bioavailable small-molecule inhibitor of BCL-2, an anti-apoptotic protein. Based on evidence demonstrating improvement in progression-free survival (PFS) and overall survival (OS),¹⁻³ it has been approved in Canada for various regimens in the treatment of CLL and AML (i.e., venetoclax monotherapy, venetoclax/obinutuzumab and venetoclax/rituximab for CLL and venetoclax/azacitidine for AML). Initiation of venetoclax can be complicated as it requires ramp-up dosing with bloodwork and hydration to reduce the risk for tumor lysis syndrome (TLS). This article will focus on providing guidance during the initiation of venetoclax, particularly in resource limited centres.

Patient Preparation

The basis for successful treatment is dependent on how well a patient is informed about their treatment plan. It should be noted that when following the ramp up schedule with frequent lab monitoring, most patients can be managed effectively as outpatients with TLS largely being limited to those with biochemical aberrations. TLS is more prevalent in the CLL population than the AML population. During the initiation of venetoclax, patients will require multiple visits (daily or weekly depending on the protocol) for bloodwork and hydration, which can be particularly challenging for

patients in rural areas who must arrange transportation and accommodation. Social workers are a valuable resource for connecting patients with assistance programs to help cover the costs of transportation and accommodation. It is important to provide patients with both written and verbal information on the venetoclax schedule, as well as information on side effects management. When venetoclax is used in combination with other agents, patients are provided with a written medication calendar outlining the required supportive pre-medications.

Standard Protocol to Prevent Subjective Variation

Initiating venetoclax requires a multidisciplinary approach. It is prudent that each team member follows the same protocol to reduce the chance of error. We follow the Alberta Health Services protocols for venetoclax initiation at our centre. Standardized protocols aid in minimizing the risk of error when various nurses see the patient at each visit.

Assessment for the Risk of Tumor Lysis Syndrome (TLS)

Clinical TLS is defined by clinical manifestations, most commonly renal, cardiac or neuromuscular, induced by worsening of the metabolic and electrolyte abnormalities in laboratory test results.⁴ The risk of TLS depends on the initial lymphocyte count and the extent of lymphadenopathy (**Figure 1**).⁶ Due to the limitations of physical examinations, it is recommended to arrange a CT scan of neck, chest, abdomen, and pelvis to better assess overall lymphadenopathy.⁵ In addition, renal function is an important predictor for TLS, and patients with creatinine

clearance <80 mL/min are at relatively higher risk of developing TLS.⁷

Supportive Medications and Drug Interactions

1. Anti-infective prophylaxis:

The incidence of opportunistic infections with venetoclax is approximately 3.1%.⁸ The British Columbia Cancer Agency (BCCA) drug manual and product monograph for venetoclax do not recommend pneumocystis jirovecii pneumonia (PJP) and/or shingles prophylaxis. The BCCA protocol for venetoclax/obinutuzumab recommends PJP and anti-viral prophylaxis for lymphoma patients only during periods of grade 3/4 neutropenia.⁹ Due to the lack of strong evidence, many centers have their own protocol for anti-PJP and anti-shingles prophylaxis. For AML patients, anti-infective prophylaxis for bacterial, viral, and fungal infections is considered for all patients with an ANC of

<500/ μ L.⁹ PJP prophylaxis includes sulfamethoxazole and trimethoprim. For patients allergic to the sulfa group of drugs, dapsone or atovaquone are other alternatives. For shingles prophylaxis, we use valacyclovir. Hepatitis B screening is recommended prior to initiating chemo/immunotherapy.⁹

2. TLS prophylaxis:

All patients require prophylaxis for TLS using oral hydration and anti-hyperuricemia agents in an outpatient setting beginning 48 and 72 hours prior to initiation of therapy, respectively. Hospitalization is recommended for high-risk patients, medium risk patients with abnormal CrCl, and any at-risk patients with CrCl $\leq$ 50 mL/min. Hospitalization may be considered for those with additional risk factors for TLS (CrCl $\leq$ 80 mL/min; unable to drink 1.5-2 L per day; unsuitable for outpatient treatment and lab monitoring; or at physician discretion).⁹

3 STEPS: ASSESS, PREPARE, INITIATE

The 5-week ramp-up dosing schedule is designed to gradually reduce tumor burden (debulk) and decrease the risk of TLS

STEP 1: ASSESS PRIOR TO VENETOCLAX	STEP 2: PREPARE 2-3 DAYS PRIOR TO FIRST DOSE	STEP 3: INITIATE FIRST 5 WEEKS OF TREATMENT
Treatment: Tumor burden assessment; blood	Anti-hyperuricemics ^a	Hydration ^b
LOW TUMOR BURDEN All LN <5 cm AND ALC <25 $\times$ 10 ⁹ /L	 Allopurinol	Oral (1.5-2 L) 
MEDIUM TUMOR BURDEN Any LN 5 cm to <10 cm OR ALC $\geq$ 25 $\times$ 10 ⁹ /L	 Allopurinol	Oral (1.5-2 L)  Consider additional IV
HIGH TUMOR BURDEN Any LN $\geq$ 10 cm OR Any LN $\geq$ 5 cm AND ALC $\geq$ 25 $\times$ 10 ⁹ /L	 Allopurinol Consider rasburicase if baseline uric acid is elevated	Oral (1.5-2 L)  and IV (150-200 mL/hr as tolerated) 
		Outpatient • For first dose of 20 mg and 50 mg: predose, 6-8 hours, 24 hours • For subsequent ramp-up doses: predose Outpatient • For first dose of 20 mg and 50 mg: predose, 6-8 hours, 24 hours • For subsequent ramp-up doses: predose • For first dose of 20 mg and 50 mg: consider hospitalization for patients with CrCl <80 mL/min; see below for monitoring in hospital In hospital • For first dose of 20 mg and 50 mg: predose, 4, 8, 12, and 24 hours Outpatient • For subsequent ramp-up doses: predose, 6-8 hours, 24 hours

Step 1: Assess tumor burden, renal function, and comorbidities (CrCl <80 mL/min), and assess and correct baseline blood chemistries^a

Step 2: Begin administering antihyperuricemics 2-3 days prior and initiate oral and/or IV hydration 2 days prior^b

Step 3: Initiate 5-week dose ramp-up^c and monitor blood chemistry (review in real time). For 1L treatment, initiate the ramp-up on cycle 1, day 22^d

The risk of TLS may decrease as tumor burden decreases

Figure 1. TLS risk categories and prophylactic measures for venetoclax-based treatment in CLL⁶

Rasburicase can be considered for high-risk patients with an elevated uric acid level at baseline. With appropriate out-patient support, most patients do not need hospitalization for bloodwork.

3. Drug interactions:

CYP3A4 inducers may decrease serum concentration of venetoclax. P-glycoprotein inhibitors (P-gp) may increase serum concentration of venetoclax.^{10,11} Dose adjustment for venetoclax is necessary, especially in the treatment of AML in combination with azacitidine, to reduce the risk of severe cytopenia (primarily neutropenia). For the management of CLL, concurrent administration of therapeutic agents which are strong CYP 3A4 inhibitors is contraindicated at initiation and during the dose ramp-up phase due to increased serum concentration of venetoclax and potential increased risk of TLS.

Initiating Venetoclax: Ramp-up Phase:

During the early development of venetoclax in CLL, TLS events led to two deaths prior to adoption of the current 5-week ramp-up period: one death after an initial 50 mg venetoclax dose,¹² and one following a 1,200 mg dose.¹⁴ To mitigate TLS risk, modifications including TLS risk-stratification, prophylaxis, monitoring, and initiating with a lower dose (20 mg) were introduced to subsequent clinical protocols.⁸

For the venetoclax/rituximab (V/R) protocol, venetoclax is administered first and is titrated weekly starting at 20 mg upon initiation and increased up to 400 mg daily by week 5. Rituximab is initiated after the patient has completed the 5-week ramp-up of venetoclax.¹² The venetoclax/obinutuzumab protocol requires the initiation of venetoclax on Day 22 of cycle 1 after first administering obinutuzumab.¹³ Many of these patients will have had significant cytoreduction with obinutuzumab, making the ensuing venetoclax dose titration much easier. In an ongoing venetoclax and obinutuzumab trial involving patients with CLL and comorbid conditions, all documented TLS cases were in the obinutuzumab arm of the regimen prior to the initiation of venetoclax therapy. The weekly ramp up-protocol is the same as with V/R. Due to the more acute nature of AML compared to CLL, the venetoclax dose ramp-up is condensed to 3 days in combination with azacitidine.³

Side Effects Management

1. Tumor lysis syndrome:

Monitoring laboratory investigations for TLS and the management of abnormalities during venetoclax-based therapy is performed differently at various centres depending on the available resources.

In tertiary centres with available services, the pharmacy team is often utilized for monitoring and management of TLS-related issues. In centres where resources are limited, a team-based approach, led by the treating physician is often utilized.

For abnormal blood chemistry including elevated potassium; low calcium; elevated phosphate; elevated uric acid and/or elevated creatinine, the recommendation is to withhold venetoclax and the associated drug in the treatment regimen for CLL. Blood chemistry abnormalities must be corrected prior to its administration. If they resolve within 24-48 hours venetoclax may be re-initiated with the associated drug in the regimen.⁹ Mild aberrations in chemistry are common and can be followed if no clinical concern of TLS is present.

For abnormal blood chemistry lasting more than 48 hours or in the case of clinical TLS (the presence of laboratory TLS plus any of the following: cardiac arrhythmia; symptomatic hypocalcemia seizures; increased creatinine level of 26.5 μ M; or a single value greater than 1.5 times the upper limits of normal), the BCCA protocol recommends withholding the venetoclax-based regimen. Once the abnormalities have been corrected, venetoclax may be re-initiated at a lower dose as shown in **Table 1**. Reduced dosing is continued for 1 week before dose escalation can resume.⁹

Venetoclax Dose at Interruption	Recommended Restarting Dose
20 mg once daily	10 mg once daily
50 mg once daily	20 mg once daily
100 mg once daily	50 mg once daily
200 mg once daily	100 mg once daily
300 mg once daily	200 mg once daily
400 mg once daily	300 mg once daily

Table 1. Dose modification for venetoclax during ramp-up phase for clinical TLS⁹

2. Neutropenia/Pancytopenia

In clinical trials, when venetoclax was administered in combination with rituximab or obinutuzumab, the rates of grade 3/4 neutropenia were 57.7% and 52.8%, respectively.^{12,13} In patients with AML who received venetoclax/azacitidine, the incidence of

grade ≥ 3 neutropenia (absolute neutrophil count (ANC) $<1000/\mu\text{L}$) was 42%.³

In CLL, the recommended management of the first episode of grade 3 neutropenia and fever or grade 4 neutropenia (ANC $< 500/\mu\text{L}$) is to withhold venetoclax until the neutropenia resolves; venetoclax can then be re-initiated at the same dose. If neutropenia recurs, venetoclax should be withheld again until the neutropenia resolves. Venetoclax should then be re-initiated at a lower dose as recommended in **Table 1**. A dose escalation should be attempted if the neutrophil count remains normal for 1 week.³ If grade 3 neutropenia persists, the use of granulocyte colony stimulating factor (G-CSF) may be considered often at dosing schedules of 300 μg subcutaneously, one to two times per week.

For AML-related treatment with venetoclax and azacitidine, neutropenia management depends on the remission status of the AML. AML patients with residual disease on bone marrow following cycle 1 should receive subsequent cycles of treatment with no dose interruption/delay until a repeat assessment demonstrates complete remission (CR). For patients with CR and grade 4 pancytopenia (ANC $<500/\mu\text{L}$, platelets $<25 \times 10^3/\mu\text{L}$) following cycle 1, venetoclax must be delayed until ANC and platelet count recovery or for up to 14 days. For subsequent cycles after achieving CR, patients with grade 4 pancytopenia must have the next cycle delayed until ANC and platelet count recovery is achieved or for up to 14 days. Venetoclax is administered for 21 days instead of 28 days for subsequent cycles.^{3,11}

Use in Special Populations

Pregnancy and lactation

Venetoclax should not be used during pregnancy. Females of reproductive potential should undergo pregnancy testing prior to the initiation of venetoclax. Females of reproductive potential should be advised to use effective contraception during treatment with venetoclax and for at least 30 days following the last venetoclax dose.¹⁵ Breastfeeding should be discontinued during treatment with venetoclax.¹⁵

Vaccines

Live or attenuated vaccines are not recommended during venetoclax treatment and until B-cell recovery has occurred following treatment (i.e., at least 6 months after treatment with an anti-CD20 monoclonal antibody and at least 3 months after other treatment is discontinued).⁹

Conclusion

Venetoclax has offered a new and effective option in targeted therapy for CLL and AML. Venetoclax initiation and ramp-up require TLS risk assessment, and risk-stratified monitoring and mitigation measures, which can be cumbersome but allow for universally safe initiation and dose escalation. As an oral therapy with good tolerability, it is an attractive option for the elderly patient population. An all-inclusive approach involving a well-informed patient and a multi-disciplinary medical team has the potential to help patients overcome possible initial hurdles in the long-term treatment of AML and CLL.

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References

1. Al-Sawaf O, Zhang C, Tandon M, Sinha A, Fink AM, Robrecht S, Samoylova O, Liberati AM, Pinilla-Ibarz J, Opat S, Sivcheva L. Venetoclax plus obinutuzumab versus chlorambucil plus obinutuzumab for previously untreated chronic lymphocytic leukaemia (CLL14): follow-up results from a multicentre, open-label, randomised, phase 3 trial. *The Lancet Oncology*. 2020 Sep 1;21(9):1188-200.
2. Kater AP, Kipps TJ, Eichhorst B, Hillmen P, D'Rozario J, Owen C, Assouline SE, Lamanna N, Robak TJ, de la Serna J, Jaeger U. Five-year analysis of murano study demonstrates enduring undetectable minimal residual disease (uMRD) in a subset of relapsed/refractory chronic lymphocytic leukemia (R/R CLL) patients (Pts) following fixed-duration venetoclax-rituximab (VenR) therapy (Tx). *Blood*. 2020 Nov 5;136:19-21.
3. DiNardo CD, Jonas BA, Pullarkat V, Thirman MJ, Garcia JS, Wei AH, Konopleva M, Döhner H, Letai A, Fenaux P, Koller E. Azacitidine and venetoclax in previously untreated acute myeloid leukemia. *New England Journal of Medicine*. 2020 Aug 13;383(7):617-29.
4. Cairo MS, Coiffier B, Reiter A, Younes A, TLS Expert Panel. Recommendations for the evaluation of risk and prophylaxis of tumour lysis syndrome (TLS) in adults and children with malignant diseases: an expert TLS panel consensus. *British journal of haematology*. 2010 May;149(4):578-86.
5. Fischer K, Al-Sawaf O, Hallek M. Preventing and monitoring for tumor lysis syndrome and other toxicities of venetoclax during treatment of chronic lymphocytic leukemia. *Hematology* 2014, the American Society of Hematology Education Program Book. 2020 Dec 4;2020(1):357-62.
6. Waggoner M, Katselos J, Thomas E, Galinsky I, Fox H. Practical Management of the Venetoclax-Treated Patient in Chronic Lymphocytic Leukemia and Acute Myeloid Leukemia. *Journal of the Advanced Practitioner in Oncology*. 2022 May;13(4):400.
7. Davids MS, Hallek M, Wierda W, Roberts AW, Stilgenbauer S, Jones JA, Gerecitano JF, Kim SY, Potluri J, Busman T, Best A. Comprehensive Safety Analysis of Venetoclax Monotherapy for Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia Safety of Venetoclax Monotherapy in Relapsed/Refractory CLL. *Clinical Cancer Research*. 2018 Sep 15;24(18):4371-9.
8. BC Cancer Protocol Summary for Treatment of Previously Untreated Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma using Venetoclax and Obinutuzumab. http://www.bccancer.bc.ca/chemotherapy-protocols-site/Documents/Lymphoma-Myeloma/LYVENOB_Protocol.pdf.
9. Wei AH, Montesinos P, Ivanov V, DiNardo CD, Novak J, Laribi K, Kim I, Stevens DA, Fiedler W, Pagoni M, Samoylova O. Venetoclax plus LDAC for newly diagnosed AML ineligible for intensive chemotherapy: a phase 3 randomized placebo-controlled trial. *Blood*. 2020 Jun 11;135(24):2137-45.
10. Seymour JF, Kipps TJ, Eichhorst B, Hillmen P, D'Rozario J, Assouline S, Owen C, Gerecitano J, Robak T, De la Serna J, Jaeger U. Venetoclax-rituximab in relapsed or refractory chronic lymphocytic leukemia. *New England Journal of Medicine*. 2018 Mar 22;378(12):1107-20.
11. Fischer K, Al-Sawaf O, Bahlo J, Fink AM, Tandon M, Dixon M, Robrecht S, Warburton S, Humphrey K, Samoylova O, Liberati AM. Venetoclax and obinutuzumab in patients with CLL and coexisting conditions. *New England Journal of Medicine*. 2019 Jun 6;380(23):2225-36.
12. Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, Chow LQ, Vokes EE, Felip E, Holgado E, Barlesi F. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *New England Journal of Medicine*. 2015 Oct 22;373(17):1627-39.
13. Venclexta® Product Monograph. https://pdf.hres.ca/dpd_pm/00046366.PDF

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