ROSALIND FRANKLIN UNIVERSITY OF MEDICINE AND SCIENCE COLLEGE OF PHARMACY STUDENT WRITING CLUB:

The Pharmacist's Role in New Acute Myeloid Leukemia Treatments

by Maximilian Vitas, 2022 PharmD Candidate, Shujie Lin, 2022 PharmD Candidate, Rucha Kulkarni, 2023 PharmD Candidate

Abstract

Newly approved agents such as gemtuzumab, midostaurin, gilteritinib, and venetoclax have created a shift in current treatment practices for acute myeloid leukemia (AML). These agents have evidence for improving AML patient outcomes and act as targeted therapy for specific AML subtypes. Pharmacists hold critical roles in evaluating the safety and use of these new agents as well as the cancer continuum of AML.

Acute myeloid leukemia (AML) is one of four leukemia subtypes that affect myeloid stem cells. This cancer accounts for 1.1% of all new cancer cases in the United States and yields a 28.7% 5-year survival from diagnosis, which is 35% less than the average 5-year survival rate for all leukemia types.[1] Compared to other cancers, AML has the most expensive initial 1-year treatment costs, averaging $182,900 (the next most expensive are cancers of the brain, which average $134,400).[2] With a mean age of 68 at diagnosis, AML is considered a cancer of the elderly; however, it can affect all ages.[1] The death rate of AML has steadily decreased, from 8.36 deaths per 100,000 cases in 1980, to 6.27 in 2016. This decrease is due in part to recent treatment advances and pharmacist intervention in an interdisciplinary team.

In Wisconsin, the most recent census data shows that the state population of individuals aged ≥65 increased by 2.1% over the last 10 years.[3,4] With a growing elderly population, there is cause for concern about growing cancer incidence. Public health data for age-adjusted rates surrounding AML from the Wisconsin Department of Health Services estimated a rate of 4.7 AML cases per 100,000 individuals for 2012 to 2016.[4] With a current state population of 5,822,434, an estimated 274 new AML cases will occur every year.[3] Though the number of cases is numerically low, the expected healthcare burden is an estimated $50,114,600 in direct treatment costs per year.

As part of the interdisciplinary healthcare team, pharmacists hold an important role in both treating patients and addressing the financial burden of treatment. Pharmacists' knowledge of medication use, oversight, and treatment management is paramount in patient health outcomes. With the recent approval of new AML agents such as gemtuzumab ozogamicin, midostaurin, gilteritinib, venetoclax, and more in the pipeline, the pharmacist's expertise serves to guide the cancer continuum team. In this article, the authors attempt to provide a brief overview of AML and discuss both new treatments and the contributions of the pharmacist in AML care.

AML Overview and Mutational Analysis

Acute myeloid leukemia is a hematological malignancy characterized by abnormal differentiation and proliferation of immature myeloid cells.[5] The gold standard for the diagnosis of AML is an examination of peripheral blood smears with confirmation performing a needle aspiration and biopsy of marrow from the iliac crest.[6] The most frequent subtype presentation is M2, accompanied by weakness and bleeding abnormalities.[5] Since AML is a highly variable disease, the clinical presentation may include multiple nonspecific signs and symptoms. These symptoms may include fever, weight loss, and anorexia, and can manifest as sternal discomfort with pancytopenic phenomena.[5,7] In rare cases, leukocytic infiltration resulting in disseminated intravascular coagulation causes risk for intracranial hemorrhaging; this is a common occurrence in the M3 and M5 subtypes, which contributes to the leading cause of death in AML patients.[8-10]

The primary pathogenesis of AML results from chromosomal translocations. Exact mechanisms for chromosomal alterations are not completely understood; however, these abnormalities involve improper or unusual rearrangements of chromosomes resulting in protein alterations that affect myeloid stem cell maturation.[11] The most common translocations, t(15;17), t(8;21), and inv(16), account for 3%-10% of abnormalities found.[12,13] In addition, there are a host of mutations that can alter AML prognosis.

Mutational analysis involves the pharmacogenomic process of determining patient prognostic factors; this is done by examining genetic mutations. By recommending the use of this gene-guided therapy, pharmacists take charge in seeking the best treatment outcomes for their patients through the selection of targeted therapies. For those with AML, cytogenetics play a role in assessing disease progression, prognosis, and therapy. With recently approved agents, mutational analysis is

crucial in assessing the appropriateness of treatment. In 2016, a study conducted by Papaemmanuil and colleagues enrolled 1,540 patients with AML into three prospective trials. The investigators were determined to identify AML genotypes and subsequent treatment outcomes. Upon completion of the study, a total of 5,234 driver mutations were identified across the population, with 96% of patients having at least one mutation and 86% having at least two.[14] One of the most frequent mutations was for FMS-like tyrosine kinase 3 (*FLT3*), which is a target of therapy by both midostaurin and gilteritinib.

The transmembrane tyrosine kinase *FLT3* stimulates cell proliferation by activating multiple signaling pathways. Mutations in *FLT3* genes represent one of the most common mutations found in AML and occur at an approximate frequency of 5-25% of cases.[15,16] There are two main *FLT3* subtype mutations: *FLT3* internal tandem duplication (*FLT3*-ITD) and the *FLT3* tyrosine kinase domain (*FLT3*-TKD).[17] Formally, *FLT3* mutations irregularly activate tyrosine kinase causing the proliferation of malignant cells. Mutations in *FLT3* are also difficult to detect upon diagnosis. Because of these two factors specifically, *FLT3* mutations are shown to have high rates of recurrence and relapse. These factors are also why the National Comprehensive Cancer Network (NCCN) clinical practice guidelines characterize patients with *FLT3* mutations as having poor-risk disease due to reduced overall survival and increased risk of relapse.[18] Despite this risk assessment, both midostaurin and gilteritinib have shown promising results in practice, and there is evidence that both venetoclax and gemtuzumab positively affect patients with *FLT3* mutations.

Supportive Care

Comprehensive leukemia treatment is intense and can greatly affect quality of life. Treatment is not as simple as receiving induction and consolidation therapy; it requires a full examination of current and potential adverse events, drug interactions, and efficacy monitoring by pharmacists. With new agents, both neutropenia and tumor lysis syndrome (TLS) are adverse reactions of high concern. As a result, the management of these adverse reactions by a pharmacist is extremely important.

Neutropenia is the first major concern, due to a high risk for infection following neutrophil depletion resulting from treatment. While the nadir period following induction is an expectation for treatment, many newer and more poorly understood agents, such as gilteritinib and venetoclax, must be strictly monitored for tolerability. In clinical practice, the American Society of Clinical Oncology and the Infectious Diseases Society of America both recommend prophylactic regimens for patients predicted to experience profound neutropenia while in nadir, in order to reduce treatment complications.[19] This regimen consists of fluoroquinolones, triazoles, or echinocandins, and a nucleoside analog for bacterial, fungal, and viral prophylaxis, respectively. This regimen is complicated, so the pharmacist must assess patient data to offer the best options for treatment. Managing the patient's medications and preventing drug interactions becomes key for patient survival during neutropenic events.

The second major concern in treatment is TLS. During chemotherapy, cytotoxic agents cause large-scale malignant cell lysis, prompting a torrent of cellular component release into the bloodstream, leading to hyperphosphatemia, hypocalcemia, hyperkalemia, and hyperuricemia.[20, 21] This imbalance causes significant damage, via nephropathy, acute renal failure, and cardiac arrhythmias.[21] According to a retrospective analysis conducted by Ejaz and colleagues, the incidence rate of TLS was found to be 26.4% among a cohort of 183 study participants and presented in 32.6% of patients deemed high-risk.[20] Other studies yielded a broader range of an aggregated 5% and 42% between all hematologic malignancies.[21,22] As the risk for TLS is high among this patient population, pharmacists can intervene by guiding treatment based on lab values related to TLS. To prevent renal complications, pharmacists can offer recommendations for regimens to the interdisciplinary team. Renal prophylaxis for TLS involves adequate intravenous hydration that starts 1-2 days prior to chemotherapy and extends up to 3 days after.[23] Hydration is not the finite management, however; the pharmacist might further advocate for the use of allopurinol or rasburicase to help prevent urate nephropathy.[21,23]

Treatment

The ultimate goal for treating patients with AML is to achieve complete remission and restore normal hematopoiesis. This involves eradicating all residual leukemia cells following the initial induction therapy. Complete remission is defined by the absence of evidence of residual leukemia in the marrow, in addition to an absolute neutrophil count >1000 cells/mm^3; a platelet count >100,000 cells/mm^3; having <5% blasts in the marrow; and transfusion independence.[11] Not every patient will achieve complete remission and may become classified as having reached partial remission (50% reduction in blasts with 5% to 25% remaining).[11,24]

Newer FDA-approved agents, such as gemtuzumab, midostaurin, gilteritinib, and venetoclax, have shown selectively improved efficacy in the treatment landscape of AML. As each of these medications has a different mechanism, there are special monitoring parameters and adverse events to take note of during treatment. From a regimen standpoint, adherence is the greatest challenge. It is well known that pharmacist intervention in medication management significantly improves adherence and therefore health outcomes.[25-27] Monitoring for adverse events is especially important for new agents, because they may impact treatment outcomes. With close follow-up, education, and monitoring practices, however, repeated and targeted interventions will continue to greatly improve adherence over time.[28-30]

Standard of Care Chemotherapy

Induction and consolidation therapy is the primary regimen for patients with AML.[18,31] The regimen consists of a 7-day continuous infusion of cytarabine and a 3-day bolus infusion of an anthracycline, followed by differing amounts of cycles of high-dose cytarabine (HiDAC) dependent on the AML subtype.[11,18] The regimen functions to block DNA synthesis with cytarabine while simultaneously inhibiting topoisomerase II with the anthracycline, after which HiDAC eliminates residual leukemic cells. For induction therapy, young and clinically stable patients with good performance status are considered the most ideal candidates. Approximately 60%

to 85% of this demographic will achieve complete remission.[7,11] In patients with both favorable and intermediate cytogenetics, the cure rate is approximately 60%-70%.[7] Patients with poor cytogenetics often do not receive the same benefit. For patients at the extremes of age, tolerability to this regimen can also be a limiting factor. In such cases, patients are more likely to achieve better clinical outcomes with targeted therapies.

Gemtuzumab Ozogamicin

Gemtuzumab ozogamicin (GO) is an older agent in the timeline of leukemia treatment. It was re-approved by the FDA in June 2020 for the treatment of newly diagnosed CD33+ AML in adults or children ≥1 month old.[32] Gemtuzumab ozogamicin acts as a powerful agent for *FLT3* mutations. It also has an indication for the treatment of relapsed or refractory CD33+ AML in adult and pediatric patients ≥2 years of age. The agent is a humanized antibody-drug conjugate, consisting of a monoclonal antibody linked to a cytotoxic molecule called calicheamicin. Mechanistically speaking, GO binds to the CD33 protein expressed on the leukemic cell surface and releases calicheamicin, causing double-strand DNA breaks and apoptosis. In the phase 3 ALFA-0701 trial, the efficacy for GO in improving event-free survival (EFS) was demonstrated at a low dose (3 mg/m^2 on days 1, 4, and 7, plus 3 mg/m^2 in two consolidation treatments) when combined with the standard of care chemotherapy.[33] In the trial, EFS was defined as the length of time to complete remission (CR) or complete remission with incomplete platelet recovery (CRP). The trial included 280 participants between ages 50 and 70 with newly diagnosed AML who were randomized 1:1 into standard of care chemotherapy vs. standard of care with GO. For participants who had achieved CR or CRP, two consolidation treatments consisting of daunorubicin and cytarabine were given with or without GO. The trial revealed that the EFS at 2 years was significantly higher in the treatment arm compared to the control group (40.8% vs. 17.1%; HR 0.58, p=0.0003). It is worth mentioning that the rate of persistent thrombocytopenia after chemotherapy was significantly higher in the GO group as well (16% vs. 3%, p<0.0001).

In clinical practice, GO is a powerful agent for those with favorable or unfavorable cytogenetics, as described by the trial. While GO does not have any certain contraindications, the product information carries a warning for hepatotoxicity and veno-occlusive liver disease (VOD), which can be fatal.[32] The incidence of VOD-related events was found to be approximately 5% in the ALFA-0701 trial, so this is an important monitoring parameter for GO use.[33] VOD is marked by increases in liver enzymes such as ALT and AST. While there are no drug interactions of note with GO, liver function test abnormalities are a common side effect of many medications, so pharmacists are a powerful resource in determining whether a patient may be suffering from VOD.

Midostaurin

Midostaurin is a first-generation *FLT3* tyrosine kinase inhibitor that was approved in 2017 as an add-on therapy for adult patients with newly diagnosed AML and an *FLT3* mutation.[34] Midostaurin has shown remarkable activity in improving overall survival with a relatively balanced safety profile. In the phase 3 RATIFY trial, patients aged 18 to 59 who had AML and an *FLT3* mutation were randomized to receive midostaurin 50 mg orally twice per day, or placebo, on days 8 through 20 following standard of care cytarabine plus daunorubicin induction, or with high-dose cytarabine consolidation, and from day 1 to 28 as a single agent for maintenance therapy.[17] Upon completion, midostaurin demonstrated significantly improved outcomes compared with placebo for median overall survival (74.7 months vs. 25.6 months) in addition to a significant improvement in median EFS (8.2 months vs. 3.0 months). The trial also showed a significant reduction in the overall risk of death by 22% in the midostaurin arm (HR 0.78, p=0.009). The RATIFY trial showed that midostaurin was equally as tolerable as the standard of care chemotherapy with similar rates of adverse events in most cases. Notably, midostaurin showed higher rates of grade 3+ anemia (92.7% vs. 87.8%, p=0.03) and rash (14.1% vs. 7.6%, p=0.008). Although grade 3+ nausea occurred less frequently with midostaurin, a higher percentage of participants in that treatment arm experienced all-grade nausea and vomiting, compared to placebo.

Pharmacists must monitor midostaurin use very carefully, as the adverse effects are intense and there can be significant consequences. One of the major adverse effects not previously highlighted is the risk of QTc prolongation. In a study conducted separately from RATIFY, patients taking midostaurin were found to experience a higher rate of QTc prolongation compared to those taking placebo (10.1% vs. 5.7% with QTc >480 ms, and 6.2% vs. 2.6% with QTc >500 ms). Based on these results, monitoring the patient's heart is extremely important. In addition, midostaurin is a CYP3A4 substrate, so co-administration of strong inhibitors, such as ketoconazole and voriconazole, or inducers such as rifampicin, can drastically alter the course of therapy.[35] To anticipate therapy-induced nausea and vomiting, the pharmacist might use prophylactic anti-emetics, such as ondansetron, olanzapine, or lorazepam prior to administering midostaurin.[36]

Gilteritinib

Gilteritinib is a tyrosine kinase inhibitor *FLT3* targeted therapy with activity against two subtypes, *FLT3*-ITD and *FLT3*-TKD. It was approved in November 2018 for the treatment of relapsed or refractory *FLT3*-mutated AML. Similar to the other agents, gilteritinib studies have established superiority in improving the overall survival of AML patients. In the phase 3 ADMIRAL trial, patients with relapsed or refractory *FLT3*-mutated AML were randomized 2:1 to receive gilteritinib monotherapy or salvage chemotherapy at the discretion of investigators.[37] Upon conclusion of the trial, the gilteritinib arm showed a significantly longer median overall survival compared to the salvage chemotherapy group (9.3 months vs. 5.6 months; HR 0.64, p<0.001). The investigators also found that the proportion of participants who achieved complete remission with full or partial hematologic recovery was remarkably higher in the gilteritinib group (34% vs. 15.3% salvage chemotherapy; 95% CI [9.8 – 27.4]).

Although gilteritinib has been shown to improve overall survival, it must be noted that the median length of exposure to gilteritinib was only 18 weeks.[37] Therefore, the long-term effects on the improvement of overall survival need to be assessed more thoroughly and the use of gilteritinib in practice should be conducted after weighing

the benefits and risks, some of which can be life threatening. In clinical trials, patients experienced differentiation syndrome, pancreatitis, and prolonged QTc intervals following treatment with gilteritinib.[38] The pertinent drug interaction with gilteritinib involves combination p-glycoprotein-CYP3A inducers which effectively reduce the efficacy of gilteritinib treatment, so it is important to check whether the patient is taking such a medication.

Venetoclax

Venetoclax is an oral oncolytic B-cell lymphoma 2 inhibitor that was approved in October 2020 to treat AML, when used in combination with a hypomethylating agent such as azacitidine, decitabine, or low-dose cytarabine (LDAC). The efficacy for this agent was determined after the completion of the VIALE-A and VIALE-C trials, which included 286 and 145 participants, respectively.[39,40] In VIALE-A, patients were randomized 2:1 to azacitidine with either venetoclax or placebo to measure improvements in overall survival and complete remission.[39] Patients who received azacitidine with venetoclax were found to have a longer median overall survival compared to the placebo counterpart (14.7 months vs. 9.6 months; HR: 0.66; 95% CI [0.52 – 0.85]). For complete remission, the azacitidine with venetoclax group was also found to have a significant improvement (37% vs. 18%; 95% CI [12 – 25]). In VIALE-C, patients were randomized 2:1 to venetoclax with LDAC or placebo with LDAC.[40] Unlike in VIALE-A, this trial's efficacy parameter was to measure the duration and rate of complete remission. The median remission time was found to be 11.1 months with venetoclax compared to 8.3 months with placebo, and the remission rate was significantly greater in the venetoclax group (27% vs. 7.4%; 95% CI [2.4 – 16]). Upon conclusion of the trial, the results from VIALE-C did not show any improvement in overall survival when venetoclax was administered with LDAC compared to placebo (p=0.114).

In clinical practice, the NCCN guidelines recommend initiation following leukocyte depletion with concomitant administration of the hypomethylating agent.[18] Because venetoclax has a high risk of causing TLS, the pharmacist must ensure that the patient is being premedicated with antihyperuricemics if needed and that monitoring is conducted every 6 hours until the risk is gone. In addition to monitoring for TLS, the pharmacist should address potential drug interactions. The dosing of venetoclax requires adjustment if the patient is taking CYP3A or P-glycoprotein inhibitors.[41] For patients with relapsed or refractory AML, antifungal prophylaxis may be necessary, in which case the risk for drug interactions increases.[18]

Waste Stewardship

The cost of treatment for AML is an estimated $50,114,600 per year and will continue to increase as more drugs are approved. In an effort to mitigate as much financial burden as possible, pharmacists hold a unique responsibility as waste stewards. Waste significantly impacts the patient and the healthcare system. A study from 2010 surveyed oncologists on the influence of cost on treatment regimens. Of those surveyed, 84% stated that cost had some effect on regimens, including adherence.[42] Oncolytic waste is present in many forms, but is common among oral agents, such as venetoclax, and patients who experience adverse events.[28,43] Previous investigations into the impact of oncolytic waste in the community setting have shown an increasing trend towards the use of oral agents when available.[28,44] For patients with AML, oral oncolytics such as azacitidine or decitabine are commonly used in the maintenance phase following consolidation.[18] Discontinuation rates of oral oncolytics can be seen up to 41%, which causes significant financial aggravation.[44] In clinical environments, waste manifests through compounding and administering intravenous preparations.[43] In the hospital however, pharmacists have more control over ideal conditions such as storage, preparation, delivery, and management. Pharmacists also are in a unique position to manage reimbursement claims for biologic medications, which significantly impacts waste. In Wisconsin, pharmacists and legislators have previously cooperated to create and operate a drug repository program under Wis. Stat. §255.056 wherein an oncolytic drug may be redistributed from an existing patient provided that the product remains in the original container, labels an expiration date within a specific time frame, and is accurately prescribed to the recipient for a valid indication.[28] Through their expertise, pharmacists are at the forefront of reducing waste both in Wisconsin and nationwide.

Conclusion

The cancer continuum of acute myeloid leukemia is both extensive and expensive. Care requires catering to patient-specific factors in order to maximize treatment outcomes. New agents, including gemtuzumab ozogamicin, midostaurin, gilteritinib, and venetoclax, present new benefits and risks in acute myeloid leukemia treatment and new challenges in therapeutic approaches. With new challenges, adherence is the key to improving health outcomes. As more agents enter the pipeline every year, it is the pharmacist's responsibility to ensure that therapy best suits the needs of the individual while simultaneously optimizing adherence and minimizing waste.

Maximilian Vitas and Shujie Lin are 4th Year Doctor of Pharmacy Candidates and Rucha Kulkarni is a Third Year Doctor of Pharmacy Candidate at Rosalind Franklin University of Medicine and Science College of Pharmacy in North Chicago, IL.

PR *This article has been peer-reviewed. The contribution in reviewing is greatly appreciated!*

Acknowledgements Thank you to Dr. Khyati Patel, Dr. Eris Tollkuci, and Dean Jolee Rosenkranz for advising and guiding our work on this project.

Disclosure: The authors declare no real or potential conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria. Dr. Eris Tollkuci is no longer affiliated with RFUMS and is employed by Sanofi Genzyme. She excluded herself from providing further guidance upon employment.

References

1. SEER cancer statistics review (CSR) 1975-2016. Surveillance, Epidemiology, and End Results Program website. Updated April 9, 2020. Accessed January 8, 2021. https://seer.cancer.gov/archive/csr/1975_2016/
2. Mariotto AB, Enewold L, Zhao J, Zeruto CA, Yabroff KR. Medical care costs associated with cancer survivorship in the United States. *Cancer Epidemiol Biomarkers Prev.* 2020;29(7):1304-1312.
3. Wisconsin profile. United States Census Bureau website. Updated 2019. Accessed January 8, 2021. https://data.census.gov/cedsci/all?q=wisconsin
4. Environmental public health tracking: Leukemia data. Wisconsin Department of

Health Services website. Updated May 2, 2018. Accessed January 8, 2021. https://www.dhs.wisconsin.gov/epht/leukemia.htm
5. Kulsoom B, Shamsi TS, Ahmed N, Hasnain SN. Clinical presentation of acute myeloid leukaemia - a decade-long institutional follow-up. *J Pak Med Assoc.* 2017;67(12):1837-1842.
6. Lagunas-Rangel FA, Chávez-Valencia V, Gómez-Guijosa MÁ, Cortes-Penagos C. Acute myeloid leukemia-genetic alterations and their clinical prognosis. *Int J Hematol Oncol Stem Cell Res.* 2017;11(4):328-339.
7. Döhner H, Weisdorf DJ, Bloomfield CD. Acute myeloid leukemia. *N Engl J Med*. 2015;373(12):1136-1152.
8. Zuckerman T, Ganzel C, Tallman MS, Rowe JM. How I treat hematologic emergencies in adults with acute leukemia. *Blood*. 2012;120(10):1993-2002.
9. Chang HY, Rodriguez V, Narboni G, Bodey GP, Luna MA, Freireich EJ. Causes of death in adults with acute leukemia. *Medicine (Baltimore).* 1976;55(3):259-268.
10. Wang ZY, Chen Z. Acute promyelocytic leukemia: from highly fatal to highly curable. *Blood.* 2008;111(5):2505-2515.
11. De Kouchkovsky I, Abdul-Hay M. 'Acute myeloid leukemia: a comprehensive review and 2016 update'. *Blood Cancer J.* 2016;6(7):e441.
12. Amanollahi Kamaneh E, Shams Asenjan K, Movassaghpour Akbari A, et al. Characterization of common chromosomal translocations and their frequencies in acute myeloid leukemia patients of northwest Iran. *Cell J.* 2016;18(1):37-45.
13. Martens JH, Stunnenberg HG. The molecular signature of oncofusion proteins in acute myeloid leukemia. *FEBS Lett.* 2010;584(12):2662-2669.
14. Papaemmanuil E, Gerstung M, Bullinger L, et al. Genomic classification and prognosis in acute myeloid leukemia. *N Engl J Med*. 2016;374(23):2209-2221.
15. Short NJ, Rytting ME, Cortes JE. Acute myeloid leukaemia. *Lancet.* 2018;392(10147):593-606.
16. Daver N, Schlenk RF, Russell NH, Levis MJ. Targeting *FLT3* mutations in AML: review of current knowledge and evidence. *Leukemia.* 2019;33(2):299-312.
17. Stone RM, Mandrekar SJ, Sanford BL, et al. Midostaurin plus chemotherapy for acute myeloid leukemia with a *FLT3* mutation. *N Engl J Med*. 2017;377(5):454-464.
18. Pollyea DA, Bixby D, Perl A, et al. NCCN guidelines insights: acute myeloid leukemia, version 2.2021. *J Natl Compr Canc Netw*. 2021;19(1):16-27.
19. Taplitz RA, Kennedy EB, Bow EJ, et al. Antimicrobial Prophylaxis for Adult Patients With Cancer-Related Immunosuppression: ASCO and IDSA clinical practice guideline update. *J Clin Oncol.* 2018;36(30):3043-3054.
20. Ejaz AA, Pourafshar N, Mohandas R, Smallwood BA, Johnson RJ, Hsu JW. Uric acid and the prediction models of tumor lysis syndrome in AML. *PLoS One.* 2015;10(3):e0119497.
21. Montesinos P, Lorenzo I, Martín G, et al. Tumor lysis syndrome in patients with acute myeloid leukemia: identification of risk factors and development of a predictive model. *Haematologica.* 2008;93(1):67-74.
22. Cairo MS, Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification. *Br J Haematol*. 2004;127(1):3-11.
23. Edeani A, Shirali A. Chapter 4: tumor lysis syndrome. American Society of Nephrology website. Published May, 2016. Accessed January 18, 2021. https://www.asn-online.org/education/distancelearning/curricula/onco/Chapter4.pdf
24. DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey L. Pharmacotherapy: A Pathophysiologic Approach, 10e. McGraw-Hill; Accessed January 18, 2021.
25. Milosavljevic A, Aspden T, Harrison J. Community pharmacist-led interventions and their impact on patients' medication adherence and other health outcomes: a systematic review. *Int J Pharm Pract*. 2018;26(5):387-397.
26. Kandemir EA, Bayraktar-Ekincioglu A, Kilickap S. Assessment of adherence to cancer-associated venous thromboembolism guideline and pharmacist's impact on anticoagulant therapy. *Support Care Cancer.* 2021;29(3):1699-1709.
27. Birand N, Boşnak AS, Diker Ö, Abdikarim A, Başgut B. The role of the pharmacist in improving medication beliefs and adherence in cancer patients. *J Oncol Pharm Pract.* 2019;25(8):1916-1926.
28. Vitas M, Kloc P. Specialty pharmacy: challenging oncolytic waste. *J Pharm Soc Wis. 2*020;4:32-35.
29. Stokes M, Reyes C, Xia Y, Alas V, Goertz HP, Boulanger L. Impact of pharmacy channel on adherence to oral oncolytics. *BMC Health Serv Res.* 2017;17(1):414.
30. Bowles H, Tawfik B, Abernathy J, Lauer R, Hashemi N, Dayao Z. Pharmacist-driven oral oncolytic medication education and consent. *JCO Oncol Pract*. 2020;16(10):e1209-e1215.
31. Döhner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood.* 2017;129(4):424-447.
32. MYLOTARG. Package Insert. Pfizer Inc. 2017.
33. Castaigne S, Pautas C, Terré C, et al. Effect of gemtuzumab ozogamicin on survival of adult patients with de-novo acute myeloid leukaemia (ALFA-0701): a randomised, open-label, phase 3 study. *Lancet.* 2012;379(9825):1508-1516.
34. RYDAPT. Package Insert. Novartis Pharmaceuticals Corporation. 2017.
35. Schlafer D. Management of midostaurin-CYP3A4 drug-drug interactions in patients with acute myeloid leukemia. *Oncology (Williston Park)*. 2019;33(7):629381.
36. Abbas HA, Alfayez M, Kadia T, Ravandi-Kashani F, Daver N. Midostaurin in acute myeloid leukemia: an evidence-based review and patient selection. *Cancer Manag Res.* 2019;11:8817-8828.
37. Perl AE, Martinelli G, Cortes JE, et al. Gilteritinib or chemotherapy for relapsed or refractory *FLT3*-mutated A*ML. N Engl J Med.* 2019;381(18):1728-1740.
38. XOSPATA. Package Insert. Astellas Pharma US Inc. 2018.
39. DiNardo CD, Jonas BA, Pullarkat V, et al. Azacitidine and venetoclax in previously untreated acute myeloid leukemia. *N Engl J Med.* 2020;383(7):617-629.
40. Wei AH, Ivanov V, DiNardo CD, et al. A phase III study of venetoclax plus low-dose cytarabine in previously untreated older patients with acute myeloid leukemia (VIALE-C): a six-month update. *J Clin Oncol.* 2020;38(15):7511.
41. VENCLEXTA. Package Insert. AbbVie Inc. 2020.
42. Neumann PJ, Palmer JA, Nadler E, Fang C, Ubel P. Cancer therapy costs influence treatment: a national survey of oncologists. *Health Aff (Millwood)*. 2010;29(1):196-202.
43. Lewis J. The oncology care pharmacist in health-system pharmacy. Pharmacy Times website. Published January 15, 2017. Accessed January 19, 2021. https://www.pharmacytimes.com/publications/health-system-edition/2017/January2017/the-oncology-care-pharmacist-in-healthsystem-pharmacy
44. Monga V, Meyer C, Vakiner B, Clamon G. Financial impact of oral chemotherapy wastage on society and the patient. *J Oncol Pharm Pract.* 2019;25(4):824-830.