ASSOCIATION OF COMMUNITY CANCER CENTERS

MULTIDISCIPLINARY ACUTE LYMPHOCYTIC LEUKEMIA CARE

ENVIRONMENTAL SCAN

Association of Community Cancer Centers

TABLE OF CONTENTS

INTRODUCTION

The Association of Community Cancer Centers (ACCC) Multidisciplinary Acute Lymphocytic Leukemia Care education project focuses on identifying key barriers and challenges in caring for this patient population, as well as actionable opportunities for improving the diagnosis and management of patients with ALL across a variety of care settings. ACCC is pleased to have The Leukemia & Lymphoma Society (LLS) as a partner organization for this project. This environmental scan provides a general overview of the current landscape for ALL diagnosis and care management.

About Acute Lymphocytic Leukemia

Acute lymphocytic leukemia (ALL), also called acute lymphoblastic leukemia, represents 0.3 percent of all new cancer diagnoses in the United States.[1] In 2018, it is estimated that there will be 5,960 new cases of ALL and an estimated 1,470 people will die of this disease. ALL is the most common form of leukemia in children, but it remains the least common type of leukemia in adults. While ALL is most commonly diagnosed in people ages 15 to 39, the percent of ALL deaths is highest among people ages 65 to 74.

Historically, the French-American-British (FAB) classification divided ALL into three subtypes (L1-small, monomorphic; L2-large, heterogeneous; and L3-Burkitt-cell type). More recently, clinicians are classifying ALL as:

- B-cell ALL (subtypes include early pre-B ALL, common ALL, pre-B ALL, mature B-cell ALL)
- T-cell ALL (subtypes include pre-T ALL, mature T-cell ALL)

Of note, mixed phenotype leukemias (subtypes may include mixed lineage leukemia, ALL with myeloid markers, biphenotypic acute leukemia) are often treated with the same types of drugs used to treat ALL.

2016 WHO Classification

The 2016 World Health Organization (WHO) update to the classification of acute leukemia also incorporates recent evidence around unique biomarkers and cytogenetics-based risk assessment to better classify ALL.[2] In addition, the WHO classification includes several "provisional" descriptions including:

- B-lymphoblastic leukemia/lymphoma, BCR-ABL1–like
- B-lymphoblastic leukemia/lymphoma with iAMP21
- Early T-cell precursor lymphoblastic leukemia
- Natural killer (NK) cell lymphoblastic leukemia/lymphoma

There is no standard staging system for ALL; so, most clinicians describe ALL as untreated, in remission, or recurrent. The treatment of ALL may include chemotherapy, radiation therapy, targeted therapy, stem cell transplant, immunotherapy, or clinical trials evaluating novel approaches.

The general principles of treating patients with ALL include:

- Induction of remission
- Post-remission consolidation/intensification of therapy
- Remission maintenance (continuation therapy)

Most patients who achieve complete remission will ultimately experience relapse. Cancer clinicians need to comprehensively assess prognostic factors to guide risk-adapted treatment recommendations and the treatment decision-making process. Important prognostic factors include white blood cell count at diagnosis, disease subtype, how long it took the patient to achieve complete remission, and the presence of BCR-ABL and/or KMT2A mutations. An important additional prognostic factor is minimal residual disease (MRD) status. Quantification of MRD can provide insight into risk/benefit stratification and allow the cancer care team to make patient-specific therapeutic recommendations.

INITIAL DIAGNOSTIC WORK-UP

The initial diagnostic work-up can be challenging since adult patients with ALL often present with variable nonspecific symptoms. Some may experience constitutional symptoms such as fever and night sweats over the course of several months while others may develop an acute presentation of multiple symptoms, such as bleeding, fever, pain, dyspnea, or weakness, and require urgent hospitalization.

NCCN Guidelines

The NCCN guidelines for ALL include the following steps for work-up and risk stratification in four discrete patient groups: Ph+ ALL (AYA); Ph+ ALL (Adult); Ph- ALL (AYA); and Ph- ALL (Adult).[3] It is important to realize that the NCCN Guidelines Panel considers AYA (adolescent and young adult) to be within the age range of 15 to 39 years. However, this age range is not a firm reference point as some of the regimens within this guideline have not been tested across all ages.

2017 CAP/ASH Guideline

The 2017 College of American Pathologists (CAP)/American Society of Hematology (ASH) guideline for the initial diagnostic work-up of acute leukemia emphasizes the critical importance of ordering the right tests to reach the correct diagnosis in a timely fashion.[4] The increasing complexity of ALL diagnosis and stratification can make it difficult for clinicians to stay current with the latest evidence and expert recommendations.

The 2017 CAP/ASH guideline addresses the following key questions:

- What clinical and laboratory information should be available? (Statements 1 and 2)
- What samples and specimen types should be evaluated? (Statements 3, 4, 7, 8, and 11)
- What tests are required for all patients during the initial evaluation? (Statements 3, 5, 6, 9, and 12)
- What tests are required for only a subset of patients? (Statements 10, 13, 14, 15, 16, 17, 18, 19, 20, and 21)
- Where should laboratory testing be performed? (Statements 22, 23, and 24)

- How should the results be reported? (Statements 25, 26, and 27)

In response to these six questions, the CAP/ASH expert panel developed 27 Guideline Statements covering different types of acute leukemias; however, this report will only focus on several key statements that directly impact the diagnosis and management of patients with ALL.

Communicating Patient Information to Pathology

The CAP/ASH Guideline Statements 1 and 2 address the importance of communicating patient information (history, physical, imaging studies) to the pathologist. This information should be readily accessible by the pathologist.

- Patient information is essential for the correct diagnosis, classification, and/or determination of prognosis. However, pathologists often do not receive this information from the ordering clinician.
- Through a project focused on the integration of pathology with the cancer care team, ACCC found that pathologists in the community often do not receive nor do they have access to relevant clinical patient data.[5] Many pathologists do not have direct access to the inpatient/outpatient EHRs. After surveying pathologists, ACCC found that only 38 percent reported that they could access all medical oncology outpatient medical records.[6] In real-world community settings, order requisition forms often contain very limited patient information. Unless pathologists call the ordering clinician, they may not learn about key diagnostic or prognostic factors.
- Without critical patient information, pathologists may not know to order additional appropriate genetic or molecular testing to reach the correct diagnosis and effectively risk-stratify the disease.
- While cancer clinicians and pathologists agree that better communication is needed, current reimbursement structures do not incentivize busy clinicians to improve communication. For example, participation in tumor boards is an important way to communicate across disciplines and develop treatment plans; however, most physicians are not reimbursed for the time spent in tumor boards.

Use of Morphologic, Cytogenetic, and Molecular Tests

The CAP/ASH Guideline Statements 4, 5, 12, 14, 15 address the importance of bone marrow morphologic assessment, cytogenetic analysis, molecular genetic and/or FISH testing, and flow cytometry immunophenotyping (FCI).

- Many pathologists and clinicians in the community may have difficulty knowing which tests to order and how to interpret the results. Since most community oncologists may only see a few patients with ALL each year, they may not be up-to-date on the latest recommendations for testing.
- There are currently no standard FCI panels that are mandated for all laboratories. However, there are recommendations for instrumentation, pre-analytic variables, panel design, data analysis, and validation from several organizations.

- The NCCN Guidelines call for the use of cytogenetic analysis during the diagnostic work-up of ALL. However, many experts believe that these tests should be interpreted by qualified cytogeneticists or pathologists subspecialized in cytogenetics. Such expertise may not be readily available in different community cancer settings.
- The role of molecular genetic and/or FISH testing does not replace conventional cytogenetic analysis.
- Minimal residual disease (MRD) is a powerful prognostic predictor. Clinicians frequently have difficulty understanding the role of MRD testing since published research studies often use different testing methodology (PCR vs. flow cytometry); timing of samples; and cutoff values; as well as, measuring different outcome variables [event-free survival (EFS), relapse rate (RR), overall survival (OS)]. Cancer clinicians and pathologists need ongoing education about MRD testing. (This is further explained below in the "MRD Testing" section).
- Cytogenetic testing for t(9;22)(q34.1;q11.2); BCR-ABL1; and KMT2A (among others) is important since these prognostic factors may impact treatment decisions.
- Molecular testing for mutational analyses (e.g., PAX5, JAK1, JAK2, and/or IKZF1 for B-ALL and NOTCH1 and/or FBXW7 for T-ALL; overexpression of CRLF2 for B-ALL) may provide results that influence diagnosis, prognosis, and/or therapeutic management. These genes contribute to risk stratification, EFS, and OS.

Clinical Documentation and Communication

The CAP/ASH Guideline Statements 25 and 26 address the importance of clinical documentation that supports effective communication between the pathologist and the ordering clinician. These Statements "strongly recommend" that:

- "In the initial report, the pathologist should include laboratory, morphologic, immunophenotypic, and, if performed, cytochemical data on which the diagnosis was based, along with a list of any pending tests. The pathologist should issue addenda/amended reports when the results of additional tests become available."
- "The pathologist and treating clinician should coordinate and ensure that all tests performed for classification, management, predicting prognosis, and disease monitoring are entered into the patient's medical records."

In the real-world setting, pathology and lab reports may be difficult to find in an outpatient electronic health record (EHR). Oncologists often report that they may quickly find the original pathology report, but that it can be difficult to find updated information that may have come from cytogenetic or molecular testing since those results may come as separate reports.

Updated WHO Classification

The CAP/ASH Guideline Statement 27 recommends the use of the 2016 WHO terminology for the final diagnosis and classification of acute leukemia. The 2016 WHO revisions to the classification of acute leukemia were influenced primarily by:

- The discovery of recently identified molecular features yielding new perspectives regarding diagnostic and prognostic markers that provide novel insights for the understanding of the pathobiology of these disorders.
- Improved characterization and standardization of morphological features aiding in the differentiation of disease groups.
- A number of clinical-pathological studies that have validated the WHO postulate of an integrated approach that includes hematologic, morphologic, cytogenetic, and molecular genetic findings.

The CAP/ASH guideline also addressed the following issues pertinent to ALL:

- Assessing patients who may have CNS involvement
- Assessing patients who may have extramedullary disease

Opportunities

Based on the current state of how patients with ALL are being diagnosed in community settings, key opportunities for improvement include:

- Educate cancer clinicians regarding the different subtypes of ALL based on the 2016 WHO classification and the pertinent 2017 CAP/ASH Guideline Statements.
- Educate cancer clinicians about the role of testing for different subtypes of ALL. Provide expertise around the interpretation of complex test results when assessing prognosis.
- Improve the use of appropriate testing to properly diagnose and risk-stratify patients with ALL both in newly diagnosed patients and in the relapsed and/or refractory setting.
- Educate cancer clinicians about the NCCN ALL Guideline and its implementation in clinical practice.
- Improve clinical documentation and communication across members of the ALL cancer care team.

SHARED DECISION-MAKING

There is growing interest in applying shared decision-making (SDM) to involve patients in decisions that impact their cancer care. However, oncology clinicians may feel that they are not adequately trained to implement SDM in clinical practice, and many patients report that they are less involved than they desire to be in their cancer care decisions.[7] Studies have shown that patients who are more engaged in their healthcare decision-making are more likely to experience confidence in and satisfaction with treatment decisions and increased trust in their providers.[8] To effectively implement SDM, cancer clinicians need to understand the components of SDM and the approaches to supporting and facilitating this process as part of routine cancer care.[9]

In 2018, the National Quality Forum (NQF) developed the National Quality Partners (NQP) Playbook: Shared Decision Making in Healthcare.[10] This resource includes examples of how healthcare organizations across the country are integrating and improving SDM in clinical practice.

As clinicians diagnose and treat patients with ALL, their use of SDM may impact the selection of induction therapy; the use of stem cell transplant; approaches to relapse; enrollment in clinical

trials; and the timing of palliative care and hospice referrals. Experts on the ACCC Advisory Committee for the Multidisciplinary ALL Care project note that it may be difficult to apply SDM during the acute phase of initially treating patients who present with immediate and serious symptoms. However, after patients are stabilized, there are opportunities to explain different treatment options and engage in SDM so that patients are making informed decisions to shape personalized treatment plans that reflect their goals for treatment, values, and preferences.

Evolving Treatment Options

Ongoing scientific advances are leading to new treatment options for patients with ALL. Recent approvals include:

- In 2018, the U.S. FDA approved calaspargase pegol-mknl, an asparagine specific enzyme, as a component of a multi-agent chemotherapeutic regimen for acute lymphoblastic leukemia (ALL) in pediatric and young adult patients age 1 month to 21 years.[11]
- In 2017, the U.S. FDA approved inotuzumab ozogamicin for the treatment of adults with relapsed or refractory B-cell precursor ALL.[12]
- In 2017, the U.S. FDA granted regular approval of blinatumomab for the treatment of relapsed or refractory B-cell precursor ALL in adults and children.[13]
- In 2017, the U.S. FDA approved tisagenlecleucel for the treatment of patients up to age 25 years with B-cell precursor ALL that is refractory or in second or later relapse.[14]
- In 2018, the U.S. FDA granted accelerated approval to blinatumomab for the treatment of adult and pediatric patients with B-cell precursor ALL in first or second complete remission with MRD greater than or equal to 0.1%.[15]

Today, patients with ALL have more treatment options than ever before. Drugs that were formerly only approved for use in the relapsed/refractory setting are now moving into earlier or front-line settings. Front-line treatment for ALL may last two to three years and patients may require care from several different facilities. The NCCN guidelines recommend central nervous system (CNS) prophylaxis for all patients with ALL.[3] Most treatment options for ALL require frequent visits to the clinic and some require hospitalization. For patients considering a stem cell transplant, travel to a tertiary care center that performs stem cell transplant may add an additional burden. The potential long-term adverse effects related to treatment may include CNS impairment, peripheral neuropathy, cardiotoxicity, infertility, and an increased risk for secondary cancers.[16] Discussions about maintenance therapy may depend on whether patients were originally treated with chemotherapy versus stem cell transplant, the results of MRD testing, and other patient-specific factors. The optimal duration of maintenance therapy remains unclear, so clinicians need to properly evaluate risk and determine a follow-up schedule to assess for disease recurrence. Given the complex nature of ALL treatment, clinicians need to spend time with patients to explain potential risks and benefits associated with various therapies and the extended duration of treatment required for most patients. This time spent can help add to patients' understanding of their options and support SDM. Incorporating the individual patient's personal goals for treatment using effective patient-clinician communication strategies will facilitate SDM and lead to a more customized treatment plan.

Opportunities

Based on how SDM is currently practiced in community settings, the following represent key opportunities:

- Gather examples of successful SDM integration in the management of patients with ALL. Share these success stories with others.
- Provide guidance on SDM training and education for members of the cancer care team.
- Identify patient education materials and other tools that may facilitate the SDM process.
- Establish criteria around SDM measurement and tracking. Recruit cancer programs that are willing to pilot projects around improving SDM in routine clinical practice.

MINIMIAL RESIDUAL DISEASE TESTING

Minimal residual disease (MRD) status remains one of the most powerful predictors of progression-free and overall survival for adults with ALL. As mentioned above, the 2017 CAP/ASH guideline for the initial diagnostic work-up of acute leukemia emphasizes the importance of MRD testing when managing patients with ALL. Experts on the ACCC ALL project Advisory Committee agree that the use of MRD test results is well-established for ALL compared to other hematologic malignancies. A recent meta-analysis on MRD confirmed that in patients with ALL, "MRD status is a useful indicator of therapeutic benefit in clinical practice and has potential for making drug development more efficient by providing early evidence of treatment benefit."[17]

Current State of MRD Testing

The clinical use of MRD testing is variable in the community, and there remain differences in the timing and type of MRD tests used. While MRD testing can be done on bone marrow aspirates or peripheral blood, experts on the Advisory Committee for the ACCC Multidisciplinary ALL Care project agree that it is best to use bone marrow. A sample of 2 to 5 mL from the first pull or early pull of the bone marrow aspirate is considered optimal for MRD testing.[18] Many cancer programs use flow cytometry or PCR-based tests to measure MRD, but this may be changing as newer testing methods emerge. On September 28, 2018, the FDA approved the first NGS-based test to detect MRD in patients with ALL or multiple myeloma.[19] Currently, there is no single standardized way of performing MRD testing in patients. Different MRD testing methods continue to be studied for their specificity, sensitivity, reproducibility, efficiency, and cost.

Detection of MRD in patients with ALL may be predictive of early relapse. MRD test results also predict prognosis and the risk of relapse in patients treated with stem cell transplant.[20] The use of MRD results may impact treatment plan intensity or cause clinicians to modify treatment plans. Studies have also shown how MRD positivity at various time points after the initiation of treatment is a strong factor predicting for relapse in adults with ALL and may allow clinicians to categorize patients into high, intermediate, and low risk categories.[21]

MRD testing is also prognostic in patients who have high-risk subtypes such as the MLL/AF4 fusion gene resulting from t(4;11)(q21;q23).[22] In addition, MRD testing has also been studied in patients with ALL who have the BCR/ABL fusion gene associated with the Philadelphia (Ph) chromosome, t(9;22).[23]

Remaining Questions

Experts on the ACCC multidisciplinary ALL project Advisory Committee state that the role of MRD testing is well established in ALL, yet, there are no standards for optimal testing methods, cut-off values, etc. Experts agree that the threshold of MRD greater than 10^{-4} remains prognostic at every time point of therapy. Newer testing technologies may generate different cut-off values such as 10^{-5} or 10^{-6}. Clinicians need to know how to be confident that they are getting accurate values when they see the test report.[24] At present, it remains unknown whether serial testing of MRD after the completion of therapy may detect relapses at an earlier stage.[25] Researchers believe that residual disease is a dynamic process and the true number of residual leukemic cells may fluctuate over time.[26]

Currently, several key questions about MRD remain active areas of ongoing research:

- Which testing method is best?
- What is the optimal cut-off to define MRD positivity?
- When in the course of disease/treatment should MRD testing occur?
- Should treatment be intensified for patients who have MRD positivity?
- Should treatment intensity be reduced for patients who have MRD negativity?
- What is the value of long-term MRD surveillance after treatment completion?
- What do we know about MRD testing for the different subtypes of ALL?
- Role of serial testing of MRD
- The dynamic process of residual leukemic cells fluctuating over time

Opportunities

Based on current trends in MRD testing and its evolving science, the following are key opportunities:

- Educate cancer clinicians about different MRD testing methods, interpretation, and the use of those results to guide decision-making plans.
- Improve the use of MRD testing by ensuring that the right samples are taken, prepared, and processed for optimal results.
- Educate cancer clinicians about ways to tailor treatment plans based on MRD test results.
- Establish criteria around the use of MRD testing across different stages of treatment.
- Provide ongoing updates about the scientific and clinical advances in the use of MRD when treating patients with ALL.

PATIENT ACCESS, COST, AND REIMBURSEMENT

Experts on the ACCC Advisory Committee note that in their regions, some community oncology providers do not manage patients with ALL. Rather, they refer all patients who have acute leukemia to tertiary care centers for both initial and long-term management. Patients may also be referred to treatment centers that offer CAR T-cell therapy. The initial work-up and management of patients with ALL is time consuming and requires expertise. Some community oncology providers and cancer hospitals may not have the resources or the expertise to effectively diagnose and manage these patients. Since treatment for ALL may last a few years, patients may require that care be coordinated between a tertiary care center and a community oncology practice. Moreover, patients may experience delayed or long-term side effects that will need to be managed by community clinicians (discussed further below).

CAR T-cell Therapy

Patients who are referred for CAR T-cell therapy may risk facing significant financial burdens. Treatment with tisagenlecleucel has been priced at $475,000 and axicabtagene ciloleucel at $373,000.[27] Although many patients have health insurance coverage, they may have limited access to certain treatments such as CAR T-cell therapy. Health insurance organizations have yet to standardize national coverage policies for CAR T-cell therapy.[28] For 2019, Medicare has approved add-on payments to cover a maximum of $186,500 per case for CAR T-cell therapy.[29]

Stem Cell Transplant

Treatment options for patients with ALL may include stem cell transplant. There are nearly 200 transplant centers listed on websites like bmtinfonet.org[30] or bethematch.org.[31] The U.S. Health Resources & Services Administration (HRSA) provides historical data on transplants performed in the U.S. In 2014, there were 1,225 transplants for ALL reported to the Center for International Blood and Marrow Transplant Research (CIBMTR).[32] Selection of the transplant center is often limited by centers' contracts with patients' insurance providers. Most transplant centers have dedicated coordinators who can discuss the costs associated with stem cell transplantation and review insurance coverage. Other considerations for patients may include travel time to the transplant center, psychosocial and family support, and practical logistical concerns that may impact their ability to receive a transplant. Studies have shown that patients who undergo transplant often experience significant financial hardship.[33] In one survey, 46% of adults who had undergone a stem cell transplant reported a decrease in income following the transplant and 56% reported some type of financial hardship.[34]

Coverage for Testing

Currently, many health insurance plans cover standard diagnostic testing for ALL. Prior authorization is often required, and certain tests may not be covered.

As an example, the BlueCross BlueShield of Western New York policy states: [35]

POLICY

ACUTE LYMPHOBASTIC LEUKEMIA

BCR/ABL1 testing for messenger RNA transcript levels and size (quantitative and qualitative) prior to initiation of treatment and during therapy may be considered **medically necessary** for monitoring of Philadelphia chromosome-positive acute lymphocytic leukemia.

If BCR/ABL1 testing as above is negative, then testing for gene fusions and variants associated with Philadelphia chromosome–like acute lymphoblastic leukemia* (see Policy Guidelines) is considered **medically necessary**.

Genetic testing in acute lymphoblastic leukemia may be **medically necessary** for:

- MLL translocations and IKZF1;
- Karyotyping of G-banded metaphase chromosomes;
- KMT2A/MLL translocations.

ACUTE MYELOID LEUKEMIA

The following may be considered **medically necessary** in Acute Myeloid Leukemia (AML) in patients with normal karyotype:

- Genetic testing for FLT3 internal tandem duplication (FLT3/ITD).
- NPM1 variant testing.

Genetic testing of the following genes may be considered **medically necessary** if the leukemia has a normal karotype and FLT3 and NPM1 gene sequences contain no pathogenic variants:

- DNMT3A
- IDH1/2
- c-KIT
- CEBPA
- AML/ETO

The following genetic testing in AML is considered **investigational**:

- Genetic testing for FLT3 tyrosine kinase domain (FLT3/TKD) variants;
- Genetic testing for FLT3, CEBPA or NPM1 variants to detect minimal residual disease;
- Genetic testing for ASXL1 and RUNX1 variants.

The Centers for Medicare & Medicaid Services (CMS) National Coverage Determination (NCD) for Cytogenetic Studies (190.3) states coverage for cytogenetic tests for three subtypes of ALL: FAB L1, L2, and L3 (of note, CMS appears to be using the outdated classification system on their published NCD).[36] However, reimbursement for testing may become challenging for Medicare beneficiaries who are admitted as inpatients. The Medicare Date of Service (DOS) rule, also known as the "14-day rule," is a regulation set by CMS that requires laboratories to bill the hospital for certain clinical laboratory services and the technical component of pathology services when these are ordered less than 14 days after the patient is discharged from an inpatient hospital stay.[37] Medicare recently revised this regulation so that laboratories may bill Medicare directly for outpatient tests and procedures, instead of seeking payment from the hospital.[36]

Financial Resources

The growing recognition of the unwanted side effect of financial toxicity in cancer patients has led to research efforts and studies evaluating ways to reduce this burden on patients.[38] Yet, many patients with cancer simply remain unaware of the cost of their care.[39] While a wide range of stakeholders and health services researchers argue that oncologists need to discuss cost-related issues with patients, many clinicians do not feel adequately trained nor do they feel comfortable discussing financial matters with patients.[40]

Resources like the ACCC Financial Advocacy Network can enable cancer clinicians to proactively screen for signs of financial toxicity and implement interventions to reduce the burdens associated with cancer treatment costs. Patients may also benefit from other forms of psychosocial counseling and support as they face life-changing circumstances such as the inability to work or changes in family responsibilities. Patient advocacy organizations like The Leukemia & Lymphoma Society (LLS) (www.lls.org/support-resources) list financial resources on their websites.

Ongoing efforts are needed to enable cancer clinicians to better identify risk factors for financial distress, promote effective patient-clinician communication about the cost of cancer care, and implement supportive care models for patients and survivors who face substantial financial burden.

Opportunities

Based on the current issues that impact patient access and healthcare delivery costs, the following are several key opportunities:

- Improve communication between community cancer providers and transplant centers to facilitate timely patient referrals and access to care.
- Educate patients about resources that can improve their access to healthcare services.
- Educate cancer clinicians about the financial burdens associated with the diagnosis and treatment of ALL.
- Educate cancer clinicians about ways to utilize existing resources and provide better psychosocial supportive care services for patients with cancer who are at risk for experiencing financial toxicity.

SIDE-EFFECT MANAGEMENT

As patients undergo different phases of ALL treatment, they need careful monitoring since they may be at risk for significant side effects. In the outpatient setting, engaging the patient and their caregiver(s) is essential for early identification of and prompt intervention for common and/or severe treatment emergent adverse events. Prophylactic vaccines or medications may also be required to prevent infections. Patients who receive stem cell transplants may also require repeat vaccination or boosters. Furthermore, patients with compromised immune systems may need to avoid certain live vaccines.

As patients with ALL receive different forms of treatment, they are likely to experience a wide range of treatment-related side effects. While it is beyond the scope of this report to review all the potential side effects, the following section will focus on some of the more challenging side effects associated with the treatment of ALL:

- Tumor lysis syndrome (TLS) is an oncologic emergency that is caused by massive tumor cell lysis. Treatment and prevention of TLS requires proper risk stratification, prophylactic measures such as aggressive hydration, and prompt identification and clinical management.[41] Several different scoring systems for risk stratification may enable clinicians to provide risk-adapted prevention and management of TLS.

- Hyperleukocytosis and leukostasis is an oncologic emergency that may lead to decreased tissue perfusion. Hyperleukocytosis may be seen in up to 30% of patients with newly diagnosed ALL.[42] Symptoms may present in the CNS or the lungs, depending on the rise in viscosity and microvascular occlusion. Patients who present with signs and symptoms require emergent management by clinicians who are properly trained to provide cytoreduction, supportive care, and monitoring.
- The updated joint ASCO/Infectious Diseases Society of America (IDSA) guideline on outpatient management of fever and neutropenia in patients with cancer defines fever in neutropenic patients as a single oral temperature of ≥ 38.3°C (101°F) or a temperature of ≥ 38.0°C (100.4°F) sustained over 1 hour.[43] Febrile neutropenia may be a sign of serious infection and patients with significant hepatic or renal dysfunction are at even greater risk for life-threatening complications. Patients with ALL undergoing active treatment may require prophylactic measures based on their risk factors. Meanwhile, those patients who develop neutropenic fever need to be educated and reminded about where to go to receive appropriate and timely care.
- The cumulative effect of certain therapies may lead to long-term toxicities that may not appear for many years. Examples of such toxicities include cardiac dysfunction, neuropathy, secondary malignancies, etc. Survivorship care plans should outline how patients should be screened and monitored based on their treatment history.

Patients with ALL may also experience unique toxicities if they are treated with some of the newer agents. For example, inotuzumab ozogamicin has a risk for hepatotoxicity, and blinatumomab has a risk for neurotoxicity and cytokine release syndrome. Experts on the ACCC Advisory Committee note that mini–hyper-CVAD appears to be tolerated well in elderly patients; ponatinib plus hyper-CVAD for Ph+ ALL appears to have an acceptable level of toxicity.[44] The use of tyrosine kinase inhibitors with steroids may be an appropriate way to treat frail, elderly patients who are not fit for transplant and who may be at high risk for serious side effects.[45] The cancer care team needs to carefully coordinate how they monitor and evaluate patients who report symptoms, especially when patients are receiving care at several different facilitates.

Opportunities

Based on the current challenges associated with some treatment-related side effects, the following list outlines several key opportunities:

- Promote team-based models of care to identify and manage treatment-related side effects in a timely manner.
- Educate clinicians about effective management strategies for serious treatment-related side effects.
- Improve the coordination of vaccinations for patients receiving stem cell transplant.
- Educate patients about proactively reporting symptoms of possible treatment-emergent adverse events.

TRANSITIONS IN CARE

In many regions, patients with newly diagnosed ALL may be stabilized in a community hospital and transferred to a tertiary care center for further management. When patients return to the outpatient setting, they often require comprehensive care from a team of providers in several different settings including the community oncology practice and the tertiary care center. Patients with cancer are often overwhelmed at the time of hospital discharge and fragmented communication and lack of planning can lead to frustration and delays in care.

Several key elements must be coordinated carefully to ensure that patients with ALL are receiving optimal care. Structured discharge communication, effective patient education, and appropriate follow-up care are key. Clear instructions on their outpatient treatment regimen, points of contact, and—at a minimum— the first appointment after discharge should be provided both verbally and in writing to patients and their caregivers. Detailed discharge information should be sent to the clinicians and specialists at the outpatient clinic affiliated with the tertiary center and the local oncology practice.

While some cancer programs may rely on navigators to facilitate discharge planning and follow-up, many centers do not have dedicated navigators to guide patients who have hematologic malignancies.

Co-Management of Patients

Some patients may receive continuing treatment at their community oncology practice while others may return to the tertiary care center for outpatient care. Models of effective co-management focus on coordinating care between the tertiary care center and the local oncology practice.

One example of co-management between a tertiary care center and the local oncology practice is the "Shared Care" initiative at Dana-Farber/Brigham and Women's Cancer Center.[46] Using this model, clinicians at Dana-Farber coordinate the delivery of medical services with local oncology practices in the region.

When patients transition to the outpatient setting, all their providers (inpatient and outpatient) should have timely access to their inpatient records and be a part of the follow-up process. Patients need to be educated about the different stages of their treatment, including the role and duration of post-induction therapy. As mentioned above, patients who undergo transplant need to receive recommended vaccines at appropriate time intervals. The co-management model ensures that patients are receiving consistent education, coordinated communication, and the right preventive health services along the continuum of their cancer care journey.

Researchers note the following care coordination challenges for patients who undergo stem cell transplant:[47]

- Variations in the type of care that is provided by different cancer programs
- Variations in the patient experience
- Reimbursement challenges
- IT challenges

- Assuring a level of clinical competence for complicated clinical issues
- Paucity of community resources

Examples of strategies to improve transitions of care in oncology include:

- The use of a multidisciplinary care transition team that proactively calls patients and reviews discharge instructions[48]
- Post-discharge phone calls and follow-up appointments within 5 business days[49]
- The use of telemedicine to monitor patients or allow specialists to provide care[50]
- Care transition patient navigator who proactively anticipates and assists patients with the complexities and barriers of healthcare systems[51]
- Development of comprehensive survivorship care plans that clearly outline how patients should follow up after their treatment is completed

Opportunities

Based on the current challenges associated with transitions of care, the following are several key opportunities:

- Improve communication between clinicians working in the inpatient and outpatient settings as they coordinate follow-up care when patients are discharged.
- Educate cancer clinicians about ways to monitor and manage patients when they are discharged from the hospital.
- Find models of effective care transitions, co-management, and care coordination that can be replicated in different community settings.
- Develop standards and metrics to assess effectiveness when patients transition to the outpatient setting.
- Implement tailored care coordination models based on existing resources in the community setting.
- Educate and empower patients to play an active role in coordinating follow-up care when they leave the hospital.

SUMMARY

Numerous scientific and clinical advances are leading to more effective treatment strategies for patients with ALL. Many of these advances are closely linked to a deeper understanding of the complex biology of ALL and its various subtypes. More treatments are becoming available and tests like cytogenetics, molecular profiling, and MRD provide critical prognostic information and are guiding the development of personalized treatment plans. While clinicians at many community cancer programs may not directly manage patients with ALL during the acute phase, these providers need to be aware of current guidelines and treatment recommendations so that they can appropriately coordinate follow-up care with tertiary care cancer centers. Through the Multidisciplinary Acute Lymphocytic Leukemia Care project, ACCC will identify effective practices that address potential gaps and barriers in the community to improve the diagnosis and management of patients with ALL.

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ACKNOWLEDGEMENTS

ACCC would like to thank the Multidisciplinary Acute Lymphocytic Leukemia Care project Advisory Committee and Partner Organization for their valuable contributions.

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This project is sponsored by:

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