Innovating the Next Generation of Treatments for Blood Cancers
Executive Summary

Several studies led by hematologists at Atrium Health Levine Cancer Institute (LCI) were featured at the American Society of Hematology (ASH) annual conference, December 10 to 13, 2022. This report describes research in lymphoma, leukemia, multiple myeloma and myeloproliferative neoplasms. LCI researchers reported advances in novel treatments and combination regimens, offered data on real-world outcomes of standard-of-care treatments, and addressed disparities in treatment response and the use of supportive care. The data will help inform the development of next-generation treatments and best practices for the treatment of hematological cancers.
In Hodgkin lymphoma, which represents about 11% of all lymphomas diagnosed in the United States and is most common in people under age 35, there’s a high demand for new treatment regimens that will lessen patients’ exposure to chemotherapy and radiation. These treatments often cure the cancer but leave patients vulnerable to health complications years or even decades later.

For example, patients who receive radiation can develop cardiovascular disease or secondary cancers. LCI led a study of 83 patients with previously untreated limited-stage Hodgkin lymphoma who received three cycles of the CD30-targeting antibody drug conjugate brentuximab vedotin (Adcetris) with the chemotherapy drugs doxorubicin, vinblastine and dacarbazine. That was followed by up to eight cycles of the immunotherapy drug nivolumab (Opdivo). After completing the treatment, 100% of the participants remained alive with no evidence of active disease, with a median follow-up of 28 months. The median age of participants was 31.

Chemotherapy and radiation “can cure about 90% of patients with Hodgkin lymphoma, but we can do better,” said Dr. Steven Park, vice chair for research in the Department of Hematologic Oncology and Blood Disorders at LCI, who led the study and discussed it during an oral presentation at the ASH conference. “The idea is to maintain or improve efficacy, while at the same time minimizing long-term treatment-related complications, so our patients can go back to their lives without worrying about developing additional health problems in the future.”

LCI has participated in several trials of novel compounds to treat blood cancers, including a first-in-human study of TNB-486, an investigational bispecific antibody for non-Hodgkin lymphoma (NHL). TNB-486 targets CD19, an antigen that’s highly expressed on the surface of NHL cells. It also binds to the CD3 receptor on the immune system’s T cells, drawing the cells to lymphoma cells to boost the drug’s cancer-killing ability. TNB-486 binds to T cells with low affinity, in the hopes of reducing the risk of cytokine release syndrome, an immune response that can be severe. At ASH, preliminary data from a phase 1 study that LCI participated in was presented showing that the drug has an acceptable safety profile and was effective in patients who had a median of four prior treatments.

Another novel T-cell-engaging bispecific antibody, glofitamab, is in phase 3 trials in patients with diffuse large B-cell lymphoma (DLBCL) who relapsed after being treated with a commonly used combination of the anti-CD20 antibody rituximab (Rituxan) and chemotherapy (R-CHOP). An estimated one-third of DLBCL patients who undergo R-CHOP treatment are not cured, highlighting the need for combination approaches that could improve overall responses. Glofitamab targets CD3 and CD20, an antigen that’s prevalent on DLBCL cells. LCI
researchers participated in an international study combining glofitamab with R-CHOP in patients with previously untreated DLBCL. At ASH, they reported an overall response rate of 93.5% and minimal toxicity for the combination treatment.³

One of the newest targeted drugs to treat hematological cancers is tazemetostat (Tazverik), which was approved by the FDA in 2020 for patients with relapsed/refractory follicular lymphoma whose tumors test positive for a mutation in the gene EZH2, or who don’t have the mutation but have run out of treatment options. During a phase 1 safety trial reported at ASH, tazemetostat was tested in combination with the immune modulating drug lenalidomide (Revlimid) and rituximab. LCI was part of an international team that collected data for subsets of patients who either did or did not have mutant EZH2, were refractory to rituximab or whose disease had progressed two years after receiving a different treatment. Data presented at ASH showed that the combination treatment had a manageable safety profile and that its effectiveness was durable, even in patients without the EZH2 mutation.⁴

In multiple myeloma, LCI researchers led a first-in-human study of a novel investigational drug that works by targeting BCMA, which is expressed on nearly all multiple myeloma cells and is most abundant in malignant plasma cells. The drug, ABBV-383, is called a “trivalent” antibody, because in addition to binding to the CD3 receptor, it attaches to two BCMA domains, potentially strengthening the drug’s bond with the myeloma target. In a phase 1 study led by LCI, 124 patients were treated with one of two doses of ABBV-383 alone. At ASH, researchers reported that both doses were well tolerated, and that the overall response rate was 57%.⁵

LCI is also investigating novel combination strategies aimed at improving treatment outcomes in multiple myeloma. It is currently leading a response-adapted phase 2 study combining carfilzomib, lenalidomide, dexamethasone and daratumumab (KRd-Dara) for treatment of newly diagnosed multiple myeloma. Patients receive eight cycles of induction, followed by a treatment that is selected based on the status of minimal residual disease (MRD). Interim results from stage 1 of the study presented at ASH showed that the quadruplet drug regimen produced a 70% rate of MRD negativity using next-generation sequencing and a complete and stringent complete response rate of 65%.⁶

Importantly, the study showed that stem cell mobilization in patients eligible for stem cell transplantation was negatively impacted when stem cells were collected after eight cycles of induction. Six patients failed to mobilize an adequate number of stem cells during their first attempt. This failure rate is much higher when compared with other KRd-Dara studies that allowed stem cell mobilization after fewer cycles. Based on these results, the researchers have amended their protocol to allow collection earlier in induction. They recommend that stem cells be collected after three or four cycles of KRd-Dara. The researchers are planning further studies to better define predictive factors associated with failure of stem cell mobilization.

Real-World Treatment Outcomes

More than 186,000 people are diagnosed with leukemia, lymphoma or myeloma each year.⁷ Tracking real-world outcomes in blood cancer patients who are treated with standard-of-care regimens yields valuable insights that can help guide treatment plans for specific patient groups.

LCI led two studies focused on real-world experiences with BTK inhibitors that are used to treat several types of lymphoma. One study

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compared the newer option, acalabrutinib (Calquence), which is a twice-daily oral drug, with once-daily Ibrutinib (Imbruvica), in the first-line treatment of chronic lymphocytic leukemia (CLL). The researchers used a dataset that includes information from both electronic medical records and pharmacies, focusing on the time that elapsed between the initiation of ibrutinib or acalabrutinib and the switch to the other BTK inhibitor or the addition of a drug to slow disease progression. With a median follow up of 15 months, 94.6% of patients treated with ibrutinib as a first line treatment had not required a second line of therapy compared to 88.3% of acalabrutinib patients, the researchers reported at ASH. Since acalabrutinib is a second-generation BTK inhibitor, the findings may be surprising, said Dr. Ryan Jacobs, clinical director of the lymphoma division and hematologist-oncologist at LCI, who presented the research in an oral presentation at ASH. “We all have questions as to what the role for ibrutinib should be now,” Jacobs said. “I think that this study shows that ibrutinib might offer some advantages under some circumstances.”

In the second study, researchers found that 40% of CLL patients who switched from ibrutinib to acalabrutinib stayed on the second-generation BTK inhibitor for a significantly shorter amount of time than they had taken ibrutinib, but the reasons for the discontinuations were unclear. Jacobs said that future research will seek to better understand differences in treatment compliance between the two BTK inhibitors.

BTK inhibitors have become standard of care in the first-line treatment of CLL, as research has proven clear advantages over chemotherapy. At ASH, LCI researchers presented data from a four-year study of patients with CLL/small lymphocytic lymphoma (SLL) that investigated real-world outcomes of first-line treatment with ibrutinib versus chemotherapy. Among 363 patients treated with chemotherapy, the median time before transitioning to another treatment was 56.5 months, while the median time to next treatment for the 383 patients taking ibrutinib was not reached during the four-year study period. Adverse events were lower among patients taking ibrutinib. The researchers suggested that future analyses should examine age, comorbidities and other patient characteristics to better understand real-world outcomes in CLL/SLL patients.

Cell therapy is another next-generation treatment that is improving prognoses in some blood cancers. For patients with relapsed or refractory large B-cell lymphoma (LBCL) who are not eligible for stem cell transplants, the 2021 FDA approval of the CAR-T cell therapy lisocabtagene maraleucel, or liso-cel (Breyanzi), offered an alternative to second-line chemotherapy. In an LCI-led study presented at ASH, 61 patients who received liso-cel were compared to a real-world cohort of patients who were treated with chemotherapy. The objective response rate among the CAR-T patients was 79.6%, versus 50.5% among the control group. Could side effects portend a positive response to a drug? An LCI-led study presented at ASH suggested that may be the case with mogamulizumab (Poteligeo), a CCR4-targeting antibody that the FDA approved in 2018 to treat cutaneous T cell lymphoma (CTCL).

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Lead Investigator, Hematologist-Oncologist, Assistant Professor at LCI
The researchers analyzed 159 patients who were treated with the drug at eight academic medical centers between 2000 and 2022. They discovered that complete remissions were more common in patients who developed mogamulizumab-associated rash (MAR) than in those who did not have the side effect. The rashes were not severe in most cases and could be treated with steroids.

What’s more, 40% of patients who experienced MAR and discontinued the drug because of it still had ongoing positive responses, without needing further drug therapy. “This is one of the more surprising findings of the study,” said lead investigator Dr. Bei Hu, hematologist-oncologist and assistant professor at LCI, who discussed the study during an oral presentation at ASH. “Patients and clinicians may worry that not being on treatment will lead to disease progression, but the findings seem to suggest that you can hold mogamulizumab and not necessarily progress. I think this has the potential to be practice-changing.”

**Disparities in Treatment Response and Use of Supportive Care**

Understanding how patients’ unique characteristics impact their responses to blood cancer treatments can help oncologists select the right therapy for each patient, as well as the supportive care that’s most likely to improve outcomes. LCI clinicians presented several studies at ASH investigating the impact of psychosocial, racial and ethnic differences in patients, as well as the effectiveness of supportive care designed to address social determinants of health.

Two studies led by LCI and presented at ASH focused on the impact of distress on cancer patients. One study included patients with myeloproliferative neoplasms treated at LCI over a four-year period ending in mid-2021. Of the 141 participants, 53% reported significant
distress. Only 33% of people who self-reported a distress score of 4 or above were evaluated by social services such as psychiatry, social work and integrative oncology. Patients with distress scores of 7 or above were automatically referred to social services, but only 39% of those people were evaluated. Lead author Dr. Rushil Patel, medical oncologist at LCI, suggested that because distress is multivariable, more research is needed to better understand its causes, impact on outcomes and barriers to screening and timely referral. “We need to better integrate distress screening into the workflow, so it’s not burdensome,” he added. For example, patients could be asked to complete surveys designed to measure distress at home, prior to their appointments, he said.

In the second study, 123 patients with newly diagnosed acute myeloid leukemia (AML) were screened for depression and asked the question “Do you have insurance/financial problems or concerns?” Median overall survival in patients reporting high distress was 8.1 months, versus 19.5 months for those with moderate distress and 22.8 months among people reporting low distress. The findings prompted the authors to conclude that AML patients should be screened for distress and “early interventional approaches are urgently needed.”

LCI offers oncology nurse navigation services as part of its care model. Oncology nurse navigators can assist patients with a range of challenges, including lack of access to transportation and insurance barriers that can hamper access to care. They also refer patients to social services both within Atrium Health’s facilities and in surrounding communities.
An LCI study of AML patients presented at ASH found that the absence of oncology nurse navigation services was associated with inferior overall survival. Among 417 AML patients tracked between 2015 and 2020, 63% worked with oncology nurse navigators. (LCI started providing oncology nurse navigation services routinely to AML patients in 2018.) The researchers reported that while there were no racial or ethnic disparities in access to oncology nurse navigators or overall survival, not receiving nurse navigation was associated with inferior survival.  

Financial barriers and lack of access to transportation were among the challenges most commonly reported by participants in the study, said Dr. Brittany Ragon, assistant professor and leukemia and transplant specialist at LCI, who led and presented the research at ASH. “These are social determinants of health that add to the distress of receiving a leukemia diagnosis. Nurse navigators can identify the barriers to care and then do everything possible to provide lifeboats for our patients,” Ragon said.

LCI is coordinating with other major cancer treatment centers on a range of studies aimed at understanding how racial and ethnic differences affect responses to multiple myeloma treatments. For example, LCI led a study of outcomes in transplant-eligible Black patients with multiple myeloma who participated in a phase 2 clinical trial comparing a triplet combination of lenalidomide, bortezomib (Velcade) and dexamethasone to a quadruplet regimen of those three drugs plus daratumumab. In a presentation at ASH, LCI researchers reported that the 48-month progression-free survival rate among Black patients was lower than it was among White patients for both drug regimens. They attributed the discrepancy to higher rates of side effects in Black patients, which led to higher dropout rates.

LCI also contributed to a study investigating racial and ethnic differences in outcomes among multiple myeloma patients treated with liso-cel. They found that Black patients were more likely to experience cytokine release syndrome or prolonged cytopenias and to have longer hospital stays than Hispanic or White patients, they reported at ASH. The researchers also reported that Hispanic patients had worse overall response rates to the CAR-T therapy — 65% versus 88% in Black patients and 86% in White patients.

Peter Voorhees, LCI hematologist-oncologist and an investigator in both studies, said further investigation of treatment delivery and side effects among multiple myeloma patients who receive newer therapies will be needed to fully understand racial and ethnic disparities in response. But he said the ongoing studies focusing on disparities offer valuable guidance to hematologists treating multiple myeloma in Black patients.

“I would strongly advise them to be aggressive in preemptively treating side effects, including making dose adjustments as needed and identifying potential barriers to access to supportive care,” Voorhees said. “That will ensure that all patients are able to stay on therapy longer and enjoy longer remissions as a result.”

**Conclusion**

The development of novel therapies and combination treatments is improving outcomes in multiple blood cancers, including multiple myeloma, leukemia and lymphoma. Data presented by LCI at the 2022 ASH conference will advance efforts aimed at bringing new drugs to the clinic, as well as understanding treatment disparities and barriers to care.
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References


