# New Studies Challenge the Dogma of Blood Cancer Care

Research at #ASH22 calls into question longstanding assumptions and charts a path for gentler therapies.

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Research findings being presented during the 64th American Society of Hematology (ASH) Annual Meeting and Exposition challenge standard practices in several areas of blood cancer care and treatment. The studies offer a counterpoint to the tendency to implement ever more intensive therapies and stringent protocols and suggest that sometimes less is more.

“As researchers in hematology, we look at it as our duty to question the standard approaches that we use to treat patients, even those that we thought of as tried-and-true,” said press briefing moderator Mikkael Sekeres, MD, of the Sylvester Comprehensive Cancer Center at the University of Miami Miller School of Medicine. “These abstracts challenge some of those standards and in fact reveal that in many cases, giving less therapy and being less restrictive is actually better for patients, or at least no worse.”

Each of the studies suggest that certain therapeutics, procedures, or protocols may be omitted from the standard course of blood cancer treatment in some cases to reduce the burden on patients without compromising health outcomes.

The first study suggests that post-treatment courses of steroids may be unnecessary in patients treated with the now-standard use of high-dose methotrexate in children with acute lymphoblastic leukemia and lymphoblastic lymphoma. The second study shows that patients with relapsed or refractory acute myeloid leukemia do not derive extra benefit from undergoing intensive chemotherapy ahead of a stem cell transplant, suggesting many can proceed directly to a transplant.

The third study reveals that a restrictive diet of only thoroughly cooked food – long thought to protect patients from bacterial infections – does not reduce infection rates for patients undergoing a stem cell transplant, a finding likely to come as welcome news to patients eager to enjoy a more palatable diet. The fourth study suggests some patients with mantle cell lymphoma may be able to skip stem cell transplantation altogether thanks to the targeted drug ibrutinib.

Taken together, these studies offer opportunities to reduce the intensity, discomfort, and side

effects of cancer treatment for many patients.

High-dose methotrexate may make post-treatment steroids unnecessary for some children with ALL or LBL
(Abstract 214: High Dose Methotrexate Does Not Reduce the Risk of CNS Relapse in Children and Young Adults with Acute Lymphoblastic Leukaemia and Lymphoblastic Lymphoma. Results of the Randomised Phase III Study UKALL 2011)

The results of a new study answer some questions and raise new ones about the optimal treatment strategy for children and young adults living with acute lymphoblastic leukemia (ALL) or lymphoblastic leukemia (LBL).

The randomized study is the first to test whether the use of a shorter, higher-dose course of dexamethasone (a steroid) during the first phase of cancer treatment is associated with reduced toxicity. It also analyzed the effects of using a higher dose of the chemotherapy drug methotrexate and of omitting pulses of dexamethasone along with the chemotherapy drug vincristine monthly following initial treatment. Monthly pulses of vincristine and dexamethasone are commonly used as a "maintenance" strategy to help prevent cancer from coming back in the first few years following treatment.

The findings indicate that an initial course of daily higher dose dexamethasone (10mg/m2) spanning two weeks did not reduce toxicity compared to the standard regimen (6 mg/m2), which lasts four weeks. The results also indicate that, when given with the standard dexamethasone regimen, high-dose methotrexate reduces the risk of bone marrow but not central nervous system relapse for some sub-groups of ALL and that pulses of dexamethasone and vincristine may not have added benefit in patients who have received high dose methotrexate.

"Based on our results, if you give high-dose methotrexate after standard dexamethasone in the induction phase, omission of pulses may not reduce the chance of cure, although that conclusion should be considered tentative given the confounding interactions," said Ajay Vora, MD, of the Great Ormond Street Hospital for Children in London.

According to initial study findings, pulses were associated with an increased risk of behavior change, muscle weakness, and high blood sugar; the researchers are currently analyzing the data further to assess the effect of the pulses on quality of life.

The trial had two main phases and examined three main questions. For the first phase, researchers randomized 1,902 patients to receive either a two-week higher-dose course or a four-week course of dexamethasone during initial treatment. The results for that phase, reported in 2017, indicated the short course of steroids brought no reduction in toxicity and may be slightly less effective.

For the second phase, researchers randomized 1,570 patients to four groups: high-dose methotrexate plus dexamethasone and vincristine pulses, high-dose methotrexate without pulses, standard-dose methotrexate with pulses, and standard-dose methotrexate without pulses. Some

patients were enrolled in both phases of the trial while others only participated in one phase or the other.

Key endpoints for the second phase focused on whether the steroid pulses could be safely omitted without affecting bone marrow relapse or five-year event-free survival and whether the high-dose methotrexate could improve rates of relapse in the central nervous system.

For high dose methotrexate, the results showed no significant differences overall for most endpoints. Researchers did find a significant interaction with the dexamethasone regimen given in the first phase, with patients treated with the four-week schedule showing improvements in bone marrow relapse rates when treated with high dose methotrexate.

Overall, the results suggested that steroid pulses could be safely omitted without adversely affecting bone marrow relapse. However, omitting the pulses was associated with a decrease in event-free-survival overall. This effect was smaller in those treated with four-week dexamethasone and high dose methotrexate, suggesting it may be possible to omit pulses with this treatment schedule.

“We found that the interactions are highly significant, which is something nobody expected,” said Dr. Vora. “In addition, we were surprised that high-dose methotrexate seems to bring a benefit with respect to relapses primarily in the bone marrow and not the central nervous system, and we don’t have a biologically plausible explanation for that finding.”

Going forward, researchers will be analyzing quality of life outcomes related to the dexamethasone-vincristine pulses for further insights into the possible benefits of skipping this added therapy. They will also study outcomes at longer follow-ups to ensure these results hold. In addition, they noted that other studies are underway to further illuminate optimal treatment strategies for different patient subgroups.

Study favors immediate progression to stem cell transplant for hard-to-treat AML even without achieving complete remission first
(Abstract 4: In Patients with Relapsed/Refractory AML Sequential Conditioning and Immediate Allogeneic Stem Cell Transplantation (allo-HCT) Results in Similar Overall and Leukemia-Free Survival Compared to Intensive Remission Induction Chemotherapy Followed By Allo-HCT: Results from the Randomized Phase III ASAP Trial)

People with acute myeloid leukemia (AML) whose disease relapsed or did not respond to initial chemotherapy had similar outcomes when they proceeded directly to an allogeneic stem cell transplant (transplantation of bone marrow or peripheral hematopoietic stem cells from another person) compared with those who underwent intensive “salvage” chemotherapy (intensive chemotherapy given after leukemia returns or does not respond to initial therapy) to achieve complete remission first, according to a new clinical trial.

The findings run counter to the common practice of offering stem cell transplantation only to patients who are in complete remission, and they suggest many patients can skip the additional

step of salvage chemotherapy before receiving a transplant.

“Allogeneic stem cell transplantation is a very potent strategy which is curative for many patients,” said Johannes Schetelig, Prof. Dr. med., of the University of Dresden in Germany. “Our study suggests that the international standard of bringing patients into remission first should be questioned, as it proves that allotransplant should be considered a standard treatment option even for patients with active disease.”

Previous research has shown that patients fare better in the long run if they achieve complete remission before a stem cell transplant, but most studies have examined the question retrospectively. The new study is the first randomized trial to assess whether salvage chemotherapy makes a difference in long-term outcomes after a stem cell transplant.

Researchers from the study alliance acute leukemia and the German cooperative transplant study group, supported by DKMS, a stem cell donor center, enrolled 281 patients treated for relapsed or refractory AML in Germany. Half proceeded directly to stem cell transplantation and half underwent salvage chemotherapy first. The median time from randomization to transplant was four weeks among those proceeding directly to a transplant and eight weeks among those receiving salvage chemotherapy. Researchers tracked outcomes for a median of about three years.

The two study groups showed similar outcomes in all key endpoints. The primary endpoint, complete remission at day 56 after transplant, was achieved in 84.1% of patients in the direct-to-transplant arm and 81.3% of patients in the salvage chemotherapy arm.

The groups also had similar rates of overall survival at one year (around 70% overall survival for both groups) and three years (a bit more than 50% overall survival) after randomization. Among patients who were in complete remission at day 56, the two groups also had similar rates of leukemia-free survival at one year.

“We were astonished – we never expected these results,” Dr. Schetelig said. “Patients did not gain additional benefit from salvage chemotherapy at all. It suggests we should think about starting the process of allotransplantation as soon as possible.”

Researchers say the findings are likely to come as welcome news for patients and families, as skipping the step of salvage chemotherapy would mean avoiding the added burden of several weeks in the hospital and the cost and toxicity associated with that additional treatment. The findings could also increase the number of people eligible for stem cell transplantation.

The findings were consistent across subgroups, although researchers are continuing to analyze the data to determine whether certain subgroups of patients are more likely to benefit from one strategy versus the other. While achieving a complete remission after transplantation is within reach for the majority of patients, future research should focus on maintaining disease control over the long term, Dr. Schetlig explained.

Commonly prescribed restrictive diet is unnecessary before autologous stem cell transplantation

(Abstract 169: Non-Restrictive Diet Does Not Increase Infections in Patients with Neutropenia after Stem Cell Transplantation: Final Analysis of the Neutrodiet Multicenter, Randomized Trial)

People undergoing a stem cell transplant for cancer do not derive any benefit from a restrictive diet that is commonly prescribed to prevent infections, according to a new trial. Researchers found that patients who followed the restrictive diet, which only allows foods that have been cooked to 80° Celsius (about 175° Fahrenheit) and forbids fresh fruits and vegetables, did not have significantly lower rates of infection. People on the diet also reported a lower quality of life compared with those served a standard hospital-prepared diet.

“A protective diet is an unnecessary burden for our patients because it impairs quality of life without reducing infection incidence,” said Federico Stella, MD, of the Università degli Studi di Milano – Istituto Nazionale dei Tumori in Milan, Italy. “I think our results can be practice-changing in the context of autologous stem cell transplantation.”

In a recent survey, 90% of cancer centers reported prescribing a restrictive diet, also called a protective diet or a low-microbial diet, for patients undergoing stem cell transplants in an effort to reduce patients’ exposure to potentially harmful bacteria while their immune system is weak. The new study is the first randomized controlled trial to prospectively test the efficacy of this approach.

Researchers enrolled 247 adult patients undergoing stem cell transplantation and randomly assigned half to receive a protective diet and half to receive standard hospital food, which included the option of fresh fruits and vegetables prepared according to safe food handling procedures, as well as cold cuts and pasteurized honey and yogurt. Participants followed their assigned diet from the start of chemotherapy (administered before a transplant) until their white blood cell count recovered after the procedure.

Three-quarters of the patients underwent an autologous stem cell transplant (with stem cells from their own body) and the rest underwent an allogeneic stem cell transplant) or high-dose induction chemotherapy.

The results showed no significant difference between the two groups on any of the trial’s primary endpoints, including rates of infection and deaths during neutropenia (the period in which patients have a low white blood cell count); rates of graft-versus-host disease; feeding outcomes including length of hospitalization, nausea, or need for intravenous nutrition; or adverse events during up to 30 days following autologous transplants and 100 days following allogeneic transplants. 34% of those on the protective diet and 39% of those on the non-restrictive diet experienced infections overall. The rates of fever of unknown origin (commonly used as an indicator of infection) were also comparable between groups, occurring in 43% of patients on a protective diet and 39% of those on the non-restrictive diet.

Those assigned to the standard hospital diet reported higher satisfaction, with 35% of these

patients reporting that their “prescribed diet did not negatively impact my alimentation” compared to just 16% among those assigned to the protective diet. “The non-restrictive diet is definitely preferred by patients,” said Dr. Stella. People on the non-restrictive diet also experienced less weight loss one month after their procedure.

The researchers plan to analyze stool samples to investigate possible correlations between diet, microbiome composition, and immune system changes following stem cell transplantation.

Ibrutinib on track to replace stem cell transplantation as first-line treatment for MCL

(Abstract 1: Efficacy and Safety of Ibrutinib Combined with Standard First-Line Treatment or As Substitute for Autologous Stem Cell Transplantation in Younger Patients with Mantle Cell Lymphoma: Results from the Randomized Triangle Trial by the European MCL Network)

In a new trial of the European MCL Network, people with mantle cell lymphoma (MCL) who took the targeted cancer drug ibrutinib [Imbruvica] had rates of progression-free survival and overall survival that were on par with the current standard of care (high-dose immunochemotherapy followed by autologous stem cell transplantation), regardless of whether the patients received a stem cell transplant in addition to ibrutinib. Researchers are still awaiting data from a third comparison – between patients receiving ibrutinib plus a transplant or ibrutinib without a transplant – but say the available findings support ibrutinib over the previous standard of care.

“Based on our findings, standard chemotherapy plus ibrutinib (with or without autologous stem cell transplantation) is the new standard of care for first-line MCL patients,” said Martin Dreyling, MD, of LMU University Hospital Munich in Germany. “We have to wait for the full results; so far we don’t see any difference between these two ibrutinib curves for progression-free survival and overall survival, but already both curves are numerically superior to the old standard, autologous transplant only. I think clinicians will interpret these results as suggesting you may essentially substitute autologous transplant with ibrutinib to avoid its well-known long-term toxicities.”

The trial enrolled 870 younger adult patients (with a median age of 57 years) treated for MCL in 14 countries, primarily in Europe. One-third of the participants were assigned to receive standard care (high-dose cytarabine-containing immunochemotherapy followed by autologous stem cell transplantation and rituximab maintenance if this is the clinical routine), one-third received standard care plus ibrutinib, and one-third received ibrutinib without a stem cell transplant. Researchers tracked outcomes for a median of 2.5 years.

The primary endpoint, failure-free survival, was defined as survival without stable disease or disease progression at the end of the initial course of treatment. By this measure, standard of care was not found superior to ibrutinib without a stem cell transplant, and standard of care plus ibrutinib was found superior to standard of care alone.

In the maintenance phase of treatment, patients who received standard of care plus ibrutinib had higher rates of adverse events than patients receiving either standard of care or ibrutinib alone.

Combined with findings from other trials, researchers may conclude these results suggest ibrutinib may be best used as a replacement for, rather than an augment to, stem cell transplantation. “Even from the perspective of toxicity, the ideal regimen is a combination of conventional chemotherapy plus ibrutinib,” said Dr. Dreyling.

MCL is an aggressive cancer often diagnosed at a later stage, so many patients have a relatively poor prognosis. In addition to continuing to collect and analyze data to compare the use of ibrutinib with and without stem cell transplantation, the researchers are investigating whether factors such as particular genetic mutations or degree of cancer proliferation may influence the optimal treatment strategy. Researchers noted that the study underscores the central role of academic clinical trials in improving outcomes for patients with an otherwise dismal prognosis.

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