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HIGHLIGHTS FROM THE 63RD ANNUAL AMERICAN SOCIETY OF HEMATOLOGY MEETING & EXPOSITION LIVE & VIRTUAL CONFERENCE

DECEMBER 11–14, 2021
ATLANTA, GEORGIA

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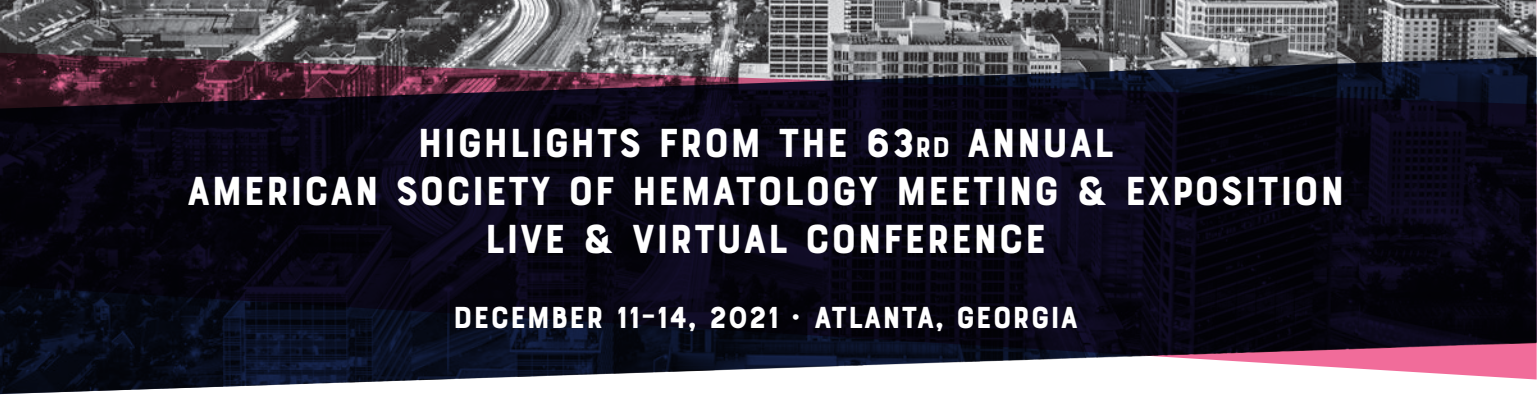

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Study Looks at Unplanned Healthcare Resource Utilization Among CAR T-Cell Therapy Recipients

While chimeric antigen receptor (CAR) T-cell therapy is a potentially life-saving option for patients with hematologic cancers, it may lead to higher use of healthcare resource utilization after infusion, according to an analysis of real-world date presented at the 2021 American Society of Hematology Annual Meeting.

Lead author Kelly Kenzik, PhD, and colleagues examined hospitalizations and emergency department (ED) visits for the first 12 months subsequent to CAR T-cell infusion to better understand health-care resource use among these patients. They used the Truven Health MarketScan database to identify commercially insured patients under the age of 65 who received CAR T-cell infusion between January 2017 and December 2019.

CAR T-cell therapy administration was discerned using ICD-10 codes as well as national drug codes for axicabtagene ciloleucel and tisagenlecleucel. Patients of interest were followed for hospitalizations and/or ED visits from CAR T-cell infusion to death, and loss of coverage at 12 months or the conclusion of the study period, whichever came first. Patient diagnoses included chronic lymphocytic leukemia (CLL), diffuse large B-cell lymphoma (DLBCL), and multiple myeloma. Overall, the study assessed 204 patients (66% male) who received CAR T-cell infusions (96% tisagenlecleucel) over the three-year analysis period.

With respect to hospitalizations, the results showed that 44% of patients had 191 hospitalizations within 12 months of CAR T-cell infusion. The investigators observed that 16% of all CLL patients, 12% of all DLBCL patients, and 11% of all myeloma patients had more than two hospitalizations. The most prevalent reasons for hospitalization were infection (41.3% of hospitalizations), myelosuppression (19.9%), and management of underlying malignancy (18.3%). Patients hospitalized for infection had the longest duration of stay per hospitalization (13.5 days), followed by management of underlying malignancy (8.3 days), and myelosuppression (5.9 days).

In terms of ED visits, the findings showed that a quarter of patients (25%) had 71 ED visits following CAR T-cell infusion. Reasons for ED visits included infections (19.7%), myelosuppression (15.5%), and cardiac emergencies (8.5%).

"The probability of these hospitalizations is highest within the first month, declining rapidly thereafter," the researchers concluded. They added that these findings "can be used to inform management strategies to mitigate unplanned healthcare utilization." ■

Source: 2021 ASH Annual Meeting, Abstract #569

Patients With B-Cell Malignancies Have High Hospital Costs Associated with Relapse

According to a study presented at the 2021 American Society of Hematology Annual Meeting, patients with mantle cell lymphoma (MCL), Waldenström macroglobulinemia (WM), marginal zone lymphoma (MZL), and chronic lymphocytic leukemia (CLL) have high hospital costs associated with disease relapse, especially among minority populations. The findings were presented by lead author Asher Chanan-Khan, MBBS, MD.

Dr. Chanan-Khan and colleagues used the Premier Healthcare Database to assess health care resource use among 23,952 CLL, 3,387 MCL, 2,655 MZL, and 1,811 WM patients in the U.S. hospital database. The population of interest were at least 18 years of age, with at least one inpatient or two hospital-based outpatient visits, and who received treatment for their conditions from January 2014 to October 2019. The researchers used descriptive analysis to assess patient sociodemographic and hospital characteristics, all-cause and lymphoma-related health care resource utilization, and costs. Costs were procured using patients' discharge files and hospital billing records.

According to the results, the average length of stay (LOS) of inpatient hospitalization ranged from 6.3 days for CLL to 7.4 days for MCL. Mean costs per hospitalization ranged from $19,566 (CLL) to $24,439 (MCL). The study found

that non-White patients have markedly longer average LOS days compared with white patients:

- CLL: 18.3 vs. 14.8
- MCL: 21.7 vs. 18.3
- MZL: 21.6 vs. 18.5
- WM: 19.0 vs. 14.5

Across the four lymphoma types, analysis showed that higher hospitals costs were correlated with patients who were non-White, Hispanic/Latino, treated in hospitals located in the Northeast or West, or had Medicaid. The investigators noted statistically significant increased costs of care for patients who received targeted therapy or supportive care, such as blood transfusions.

> **"REAL-WORLD DATA DEMONSTRATED SIGNIFICANTLY HIGHER TOTAL HOSPITAL COSTS FOR PATIENTS WITH MCL, WM, MZL, AND CLL, WITH SIGNIFICANTLY HIGHER COSTS FOR HOSPITALIZED MINORITY PATIENTS."**

"Real-world data demonstrated the significantly high total hospital costs once patients with MCL, WM, MZL, and CLL patients were hospitalized, with significantly higher impact to minority populations," the researchers concluded. They added that future studies "are needed to explore the reason for admission, clinical outcomes, and potential preventive interventions." ■

Source: 2021 ASH Annual Meeting, Abstract #3048

Oncology Advanced Practice Providers Face Constraints on Prescribing Authority

ACCORDING TO A POSTER presentation at the 2021 American Society of Hematology, prescribing chemotherapy is not a universal practice of advanced practice providers (APPs) in the oncology community. The findings were shared by Bruce E. Christensen, DSc, PA-C, of UT Health San Antonio and Mays Cancer Center. Dr. Christensen and colleagues presented the results of a survey focused on the scope of practice of APPs in oncology.

The survey was sent in January 2021 to 1,307 members of the Association of Physician Assistants in Oncology (APAO). The response rate was 11%. Of the respondents, 95% were physician assistants (PAs), 3% were nurse practitioners (NPs), and 1% were described as "other." Most respondents (87%) worked in medical oncology, but some worked in surgical oncology (6%) or radiation oncology (1%).

A total of 44% of respondents reported that they were able to independently sign chemotherapy orders, while 56% did not independently sign chemotherapy orders.

Of those who could sign orders, 60% worked in academic oncology centers and 35% worked in community oncology centers. In addition, 23% were only allowed to sign existing chemotherapy plans that did not require modifications.

Only 35% of respondents could initiate and sign new chemotherapy orders. Instead, the majority (89%) could sign existing orders. Most respondents were able to prescribe intravenous and oral medications, but only about one-third could prescribe intrathecal medications, and about half could prescribe clinical trial medications.

Of those respondents who could not prescribe chemotherapy, 74% worked in academic centers and 19% worked in a community practice. Most respondents reported no restrictions from the state medical board that would prohibit them from prescribing chemotherapy. However, 69% reported that their institution or facility did prohibit them from prescribing chemotherapy.

The survey also explored physician and employer attitudes towards APPs prescribing chemotherapy. Respondents were asked if their physician colleagues believed that limiting chemotherapy to physicians is a safety measure. About one-third reported that this was true, about one-third

that this was false, and about one-third unsure.

APPs were also asked if they thought their physician colleagues believed experienced APPs should be allowed to prescribe chemotherapy. Again, the researchers reported mixed responses: 44% agreed, 11% disagreed, and 44% were unsure.

Finally, the APPs were asked if their employer believed experienced APPs should be allowed to prescribe chemotherapy. Here, 30% reported this statement as true, 20% said it was false, and about half said they were unsure. ■

Source: 2021 ASH Annual Meeting, Abstract #1987

Study Validates IMWG Frailty Scoring in Relapsed/Refractory Multiple Myeloma

At the 2021 American Society of Hematology Annual Meeting and Exposition, Fabio Efficace, PhD, and a team of researchers presented results from a study evaluating the relevance of the International Myeloma Working Group (IMWG) Index for scoring patients with relapsed/refractory multiple myeloma. The IMWG Index has been validated for newly diagnosed multiple myeloma, but these results expand its use to those with previously treated disease.

The investigators also noted that the IMWG was able to identify distinct patient-reported health-related quality of life (HRQOL) profiles in relapsed/refractory disease, as well.

According to Dr. Efficace, the study's results "may lay the groundwork for the development of a patient-centered frailty index, which also incorporates HRQOL data, to be used in patients with relapsed/refractory multiple myeloma treated in real life."

The observational study enrolled 365 patients with relapsed/refractory multiple myeloma from 30 centers and classified them into three frailty groups: fit, intermediate-fit, and frail. The participants regularly completed validated reporting tools including the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and its myeloma module (QLQ-MY20).

Based on their IMWG frailty score at enrollment, 192 (53%), 85 (23%), and 88 (24%) patients were classified as fit, intermediate-fit, and frail, respectively. Researchers observed distinct HRQOL profiles between the three groups, which supported the IMWG's initial categorization. For example, mean EORTC QLQ-C30 physical functioning mean scores were 71.2 for fit, 62.2 for intermediate-fit, and 47.5 for frail patients ($p < 0.001$). Additionally, mean scores on the QLQ-MY20 disease symptom scale were 22.8, 25.9, and 35.9 for fit, intermediate-fit, and frail patients, respectively ($p < 0.001$). Further, the frequency of patient-reported clinically important symptoms differed significantly across the groups for pain ($p = 0.002$), dyspnea ($p = 0.004$), fatigue ($p < 0.001$), insomnia ($p = 0.022$) constipation ($p = 0.003$), and appetite loss ($p = 0.001$).

Based on the associations between the IMWG's frailty categories and the groups' respective scores on other HRQOL measures, the study's authors judged that the IMWG frailty scoring was effective in both relapsed/refractory and newly diagnosed multiple myeloma. ■

Source: ASH 2021 Annual Meeting, Abstract #115

> "[THESE STUDY RESULTS] MAY LAY THE GROUNDWORK FOR THE DEVELOPMENT OF A PATIENT-CENTERED FRAILTY INDEX ... TO BE USED IN PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA TREATED IN REAL LIFE."

Frontline Ibrutinib Plus Venetoclax Induces Deep Responses in Chronic Lymphocytic Leukemia

According to a study presented at the 2021 American Society of Hematology Annual Meeting, frontline treatment with ibrutinib in combination with venetoclax induced deep responses in patients with previously untreated chronic lymphocytic leukemia (CLL).

Researchers led by Paolo Ghia, MD, PhD, of Vita-Salute San Raffaele University in Milan, Italy, enrolled 168 patients with previously untreated CLL. The patients' median age was 58 years (range = 28-69) and the following high-risk features were identified:

- unmutated IGHV (60%)
- del17p/*TP53* mutation (20%)
- complex karyotype (19%)
- del11q without del17p (17%)

Patients up to 70 years of age received three cycles of ibrutinib lead-in followed by 12 cycles of oral ibrutinib 420 mg/day plus oral venetoclax ramp-up to 400 mg/day. Measurable residual disease (MRD) negativity was defined as undetectable MRD on two or more assessments three or more months apart using both peripheral blood and bone marrow samples. After 12 cycles of treatment with ibrutinib plus venetoclax, 149 patients were randomized to the following groups:

- confirmed undetectable MRD to placebo (n = 43)
- confirmed undetectable MRD to ibrutinib (n = 43)
- without confirmed undetectable MRD to ibrutinib (n = 31)
- without confirmed undetectable MRD to ibrutinib plus venetoclax (n = 32)

Overall median follow-up was 38.2 months (range = 15-47.9). After randomization, the median follow-up was 24 months (range = 5.8-33.1). Across all patients, the median treatment duration was 36.8 months (range = 0.5-47.9).

No new disease-free survival (DFS) events occurred in patients with confirmed undetectable MRD who were randomized to placebo or ibrutinib since the primary analysis. Post-randomization two-year DFS rates for patients with confirmed undetectable MRD were 95% for those randomized to placebo and 100% for those who received ibrutinib.

In the placebo and ibrutinib arms, estimated 36-month PFS rates were 95% and 100%, respectively. Modest improvements in complete response (CR) rates, including CR with incomplete bone marrow recovery (CRi), were observed. "The results in patients with confirmed undetectable MRD support the potential for treatment-free remission with fixed-duration treatment, including in patients with high-risk features," Dr. Ghia wrote.

For patients without confirmed undetectable MRD, greater improvements in undetectable MRD rates and CR/CRi were observed in those who received ibrutinib plus venetoclax compared with ibrutinib alone. Estimated 36-month PFS rates were 97% across both the ibrutinib and ibrutinib plus venetoclax groups.

Across all treatment arms, the most common grade 3/4 adverse events (AEs) were neutropenia (36%), hypertension (10%), thrombocytopenia (5%), and diarrhea (5%). In 13% of patients, ibrutinib or venetoclax was discontinued because of AEs. The authors concluded that "the safety profile of ibrutinib plus venetoclax was consistent with the known safety profile for each agent." ■

Source: 2021 ASH Annual Meeting, Abstract #68

> "THE RESULTS IN PATIENTS WITH CONFIRMED UNDETECTABLE [MEASURABLE RESIDUAL DISEASE] SUPPORT THE POTENTIAL FOR TREATMENT-FREE REMISSION WITH FIXED-DURATION TREATMENT, INCLUDING IN PATIENTS WITH HIGH-RISK FEATURES."

Research Supports Post-Transplant Cyclophosphamide and Tacrolimus for GVHD in Older Adults

The combination of post-transplant cyclophosphamide and tacrolimus (PTCy-TK) outperformed conventional graft-versus-host disease (GVHD) prophylaxis in patients undergoing allogeneic hematopoietic cell transplantation (alloHCT), according to a poster presented at the 2021 ASH Annual Meeting by Maria Queralt Salas, MD, from the Hospital Clinic of Barcelona in Spain.

"The continuous refinement of transplant techniques has led to a reduction of transplant-related toxicity resulting in an increasing number of alloHCT performed in older patients," the authors explained. "Since 2014, [PTCy-TK] has been progressively implemented as GvHD prophylaxis for related, matched, and mismatched unrelated donor transplantation." In this report, Dr. Salas and colleagues shared observations from the use of PTCy-TK at their institution.

Between January 2014 and June 2020, 147 adults with hematologic malignancies and who were at least 50 years old underwent alloHCT either from matched related or unrelated donor. Seventy-two (48.9%) patients received PTCy 50 mg/kg/day intravenously on day 3 and 4 after alloHCT, followed by tacrolimus, initiated at a dose of 0.03/kg/24-hour on day 5 after alloHCT. Therapy was titrated to achieve a therapeutic level of 5-15 mg/mL. Other GVHD prophylaxis strategies included calcineurin inhibitors combined with methotrexate, mycophenolate mofetil, or sirolimus.

Overall survival (OS) and GVGD-free/relapse-free survival (GRFS) were considered the main outcome variables. To analyze the independent impact of PTCy-TK prophylaxis on OS and GRFS, a multivariate Cox regression analysis was performed including GVHD prophylaxis, Disease Risk Index, and transplant year as explanatory variables, together with other variables with prognostic value in the univariate analysis.

The authors reported that the baseline characteristics were similar between each GVHD prophylaxis group. Most patients underwent alloHCT with peripheral blood (97%). Of note, 53 out of 72 patients receiving PTCy-TK were transplanted between July 2017 and December 2020, and more than 90% of patients receiving PTCy-TK had unrelated donors as their source.

For patients receiving PTCy-TK, the median of days to neutrophil (20 vs. 16; $p < 0.01$) and platelet (19 vs. 11; $p < 0.01$) engraftment were higher than for those receiving standard prophylaxis. However, the differences between the incidences of viral reactivations and infections were not statistically significant between the two groups, the researchers reported.

At 100 days post-alloHCT, the cumulative incidence of grade II-IV acute GVHD was 21.9% in the PTCy-TK group versus 21.5% in the standard GVHD prophylaxis group ($p = 0.88$). Grade III-IV acute GVHD at day 100 was 9.2% versus 9.3% ($p = 0.88$). Although the rates of aGVHD were comparable, the use of PTCY-TK resulted in a significant reduction on the incidence of moderate or severe chronic GVHD at one year (9% vs. 31.5%; $p < 0.01$).

One-year rates of OS, non-relapse mortality, and relapse were all similar between GVHD prophylaxis regimens:

- OS: 72.1% with PTCy-TK vs. 66.7% for conventional prophylaxis (hazard ratio [HR] = 0.98; $p = 0.91$)
- NRM: 18.1% vs. 13.3% (HR = 1.20; $p = 0.63$)
- relapse rates: 18.1% vs. 22.9% (HR = 0.86; $p = 0.65$)

> **"THE CONTINUOUS REFINEMENT OF TRANSPLANT TECHNIQUES HAS LED TO A REDUCTION OF TRANSPLANT-RELATED TOXICITY RESULTING IN AN INCREASING NUMBER OF ALLOHCT PERFORMED IN OLDER PATIENTS."**

"The use of this innovative combination provides superior GRFS than the use of conventional GVHD prophylaxis in older adults undergoing alloHCT, with comparable transplant-related mortality and relapse rates," the authors concluded. "GRFS is a composite endpoint considered a surrogate outcome of health-related quality of life, and the improvement of this parameter is remarkable in PTCy-TK alloHCT, especially for older patients." The findings are "encouraging," particularly when considering that older patients with hematologic disorders have a higher risk of developing transplant-related toxicity, the researchers added. ■

Source: 2021 ASH Annual Meeting, Abstract #2760

Ibrutinib Plus FCR Could Provide Functional Cure in Young CLL Patients

At more than three years of follow-up, most patients with chronic lymphocytic leukemia (CLL) who were treated with a combination of ibrutinib plus standard chemoimmunotherapy of fludarabine, cyclophosphamide, and rituximab (FCR) experienced sustained, durable responses. The benefits of this time-limited therapy approach were seen regardless of IGHV status. Matthew S. Davids, MD, from Dana-Farber Cancer Institute, presented these findings at the 2021 ASH Annual Meeting.

The authors explained that, given the excellent efficacy and tolerability of ibrutinib in a broad population of young, fit patients with CLL patients, they sought to evaluate whether time-limited ibrutinib plus chemoimmunotherapy could provide durable remission for CLL patients, irrespective of IGHV status.

In this multicenter, single-arm, phase II trial, investigators enrolled CLL patients age ≤65 years without restriction by IGHV mutation status, who met iwCLL treatment criteria. Ibrutinib 420 mg daily was given for seven days, then combined with FCR for up to six cycles. Responders continued on ibrutinib maintenance, and patients with undetectable measurable residual disease (MRD) after two years of maintenance discontinued therapy. The study's primary objective was to determine the rate of complete response (CR)/CR with incomplete hematologic recovery (CRi) with undetectable MRD two months after ibrutinib plus FCR. Secondary objectives were to assess response rates, progression-free survival (PFS) and overall survival (OS), as well as MRD negativity after two years of ibrutinib maintenance.

A total of 85 patients were enrolled at nine U.S. cites. The median age was 55 years (range = 38-65), and IGHV was unmutated in 46 of 79 evaluable patients (58.2%). del17p and TP53 mutation were present in 4 of 83 (4.8%) and 3 of 81 (3.7%) patients, respectively. The median number of FCR cycles completed was six (range = 1-6).

Dr. Davids presented data from a median follow-up of 40.3 months (range = 3.1-76), at which point the median number of ibrutinib maintenance cycles was 24 (range = 0-81). The rate of CR with undetectable MRD at any point on study is 55%, and the rate of undetectable MRD in any response was 84%. Following two years of ibrutinib maintenance, the rates of CR/CRi and undetectable MRD in patients with available data were 77% and 81%, respectively, with no differences based on IGHV status.

PFS and OS for all patients were 97% and 99%, respectively. The researchers noted that 13 of 61 patients (21.3%) who completed ibrutinib FCR and started ibrutinib maintenance while in MRD negativity have had recurrent MRD. Seven of these patients underwent retreatment with ibrutinib monotherapy (5 due to clinical progression and 2 due to recurrent MRD without clinical progression), and all seven achieved PR with retreatment.

The most common treatment-emergent grade 3/4 adverse events were hematologic, including neutropenia (40%), thrombocytopenia (32%), and anemia (11%).

Regarding these findings, Dr. Davids and coauthors concluded that, "among the few patients with recurrence after this time-limited therapy, all have responded to retreatment with ibrutinib monotherapy." The data suggest that "iFCR is worthy of exploring in comparative studies in younger, fit CLL patients who desire the possibility of functional cure with time-limited therapy." ■

Source: 2021 ASH Annual Meeting, Abstract #640

Examining Venetoclax-Based Regimen in Previously Untreated CLL

Time-limited treatment with bendamustine, rituximab, and venetoclax was associated with high rates of undetectable minimal residual disease (MRD) remission in a phase II study of adults with untreated chronic lymphocytic leukemia (CLL). These data were presented at the 2021 ASH Annual Meeting.

At data cut-off, 26 patients were enrolled, with ongoing recruitment. Patients received three cycles of induction with bendamustine and rituximab (BR) followed by consolidation with venetoclax and rituximab (VR) for a fixed one-year duration. During induction, patients received bendamustine 50 to 90 mg/m^2 for two days and rituximab 375 mg/m^2 once per 28-day cycle. Consolidation with venetoclax was initiated at 20 mg and escalated to 400 mg daily

over five weeks, followed by six cycles of VR and then five cycles of venetoclax alone.

Patients were aged a median of 60 years (range = 44-77 years), and the cohort was 61.5% male. Twenty-three patients remained on the study at a median follow-up of 12.9 months (range = 1.9-27.5), including 12 patients with at least 15 months of follow-up. The overall response rate (ORR) among these 12 patients was 100%, with 92% achieving a complete response (CR; with or without incomplete count recovery) and 8% with a partial response (PR). Three patients died on study: two deaths were related to COVID-19, and one patient developed newly metastatic squamous cell carcinoma and was taken off the study following a CR during consolidation. A response assessment in 20 patients following induction showed a 15% CR rate and an 85% PR rate after BR treatment.

> **"TIME-LIMITED TREATMENT WITH BENDAMUSTINE, RITUXIMAB, AND VENETOCLAX WAS ASSOCIATED WITH HIGH RATES OF UNDETECTABLE MINIMAL RESIDUAL DISEASE REMISSION."**

MRD evaluations in 10 patients evaluable at 16 months found undetectable MRD (<0.01%) status in 100% of peripheral blood samples and 90% of bone marrow samples. Median time to undetectable status was 12 months (range = 3-15 months) in peripheral blood and 14 months (range = 5.5-15 months) in bone marrow.

During BR induction, the most common treatment-emergent adverse events (AEs) were anemia (any grade, 21%; grade ≥3, 7%), nausea (21%; 0%), neutropenia (18%; 7%), rash (18%; 0%), constipation (14%; 0%), and transaminitis (11%; 0%). Two patients (7%) developed febrile neutropenia. Treatment-emergent AEs with venetoclax treatment included diarrhea (any grade, 36%; grade ≥3, 0%), neutropenia (21%; 11%), leukopenia (18%; 7%), and nausea (14%; 0%).

The authors noted that risk of tumor lysis syndrome (TLS) was substantially reduced after induction, with a 94% reduction of risk among patients at high or medium risk of TLS at baseline. "Of three high-risk patients at baseline, none remained high-risk after BR," they reported. Also, "of 15 medium-risk patients, only one remained medium-risk, with the remainder at low-risk." ■

Source: 2021 ASH Annual Meeting, Abstract #1555

GLOW: MRD Outcomes After Fixed-Duration Ibrutinib Combinations in Older CLL Patients

THE ALL-ORAL, ONCE-DAILY, fixed-duration combination of ibrutinib and venetoclax demonstrated superior undetectable MRD responses in older or unfit patients with previously untreated chronic lymphocytic leukemia (CLL), according to findings from the GLOW trial presented at the 2021 ASH Annual Meeting.

The GLOW trial enrolled 211 patients aged 65 years or older (or 18-64 years with cumulative illness rating scale score >6 or creatinine clearance <70 mL/min). Patients with del17p or known TP53 mutations were excluded. Participants were randomized 1:1, stratified by IGHV mutational and del(11q) status, to receive either:

- ibrutinib + venetoclax (3 cycles of ibrutinib lead-in, followed by 12 cycles of ibrutinib + venetoclax, n = 106)
- 6 cycles of chlorambucil + obinutuzumab (n = 105)

Participants' median age was 71 years, and 51.7% had confirmed unmutated IGHV, 18.0% had del11q, and 4.3% had a TP53 mutation.

MRD samples were collected for responders every 3-4 months in peripheral blood (PB) and at months nine and 18 in bone marrow (BM). MRD was evaluated using next-generation sequencing (NGS; clonoSEQ) and 8-color flow cytometry.

After a median follow-up of 27.7 months (range = 1.7-33.8) months, the rate of undetectable MRD was significantly higher in the ibrutinib + venetoclax arm than the chlorambucil + obinutuzumab arm, both in BM (51.9% vs. 17.1%; $p < 0.0001$) and in PB (54.7% vs. 39.0%; $p = 0.0259$).

In the ibrutinib + venetoclax arm, two-thirds of patients with a complete response (CR) or CR with incomplete marrow recovery (CRi) and 54.9% of patients with a partial response (PR) achieved undetectable MRD in BM. For those treated with chlorambucil + obinutuzumab, rates of CR/CRi and PR were 33.3% and 16.9%, respectively.

Researchers reported that BM undetectable MRD rates were higher for ibrutinib + venetoclax versus chlorambucil + obinutuzumab across prespecified subgroups, including patients with bulky disease, del11q, and unmutated IGHV. For the 30 patients with detectable MRD after ibrutinib + venetoclax, MRD levels remained stable for most patients from three months to 12 months after the end of treatment.

The ibrutinib + venetoclax combination also was associated with PFS rates of greater than 90% in patients with undetectable MRD, as well as patients with detectable MRD. In contrast, in the chlorambucil + obinutuzumab arm, patients with detectable MRD in PB relapsed more quickly than those with undetectable MRD. ■

Source: 2021 ASH Annual Meeting, Abstract #70

Older Patients With Newly Diagnosed CLL Benefit From Frontline Targeted Treatment

Although individuals older than 80 years make up more than 20% of cases of chronic lymphocytic leukemia (CLL), this population is underrepresented in clinical drug trials, and data on treatment outcomes are limited. At the 2021 American Society of Hematology Annual Meeting, researchers presented results from a pooled analysis of phase II and III studies of this patient population, hoping to expand the evidence base.

According to their findings, older patients with CLL experience favorable efficacy and survival outcomes with frontline targeted anti-leukemic treatments such as ibrutinib, idelalisib, and venetoclax.

The researchers pooled data from six studies conducted by the German CLL Study Group, comprising 716 total patients aged ≥80 years who received frontline treatment for CLL. The primary endpoints were overall survival (OS) and causes of death. Patients received at least one targeted agent as firstline therapy. Median follow-up was 51.8 months.

> “OLDER PATIENTS WITH CLL EXPERIENCE FAVORABLE EFFICACY AND SURVIVAL OUTCOMES WITH FRONTLINE TARGETED ANTI-LEUKEMIC TREATMENTS SUCH AS IBRUTINIB, IDELALISIB, AND VENETOCLAX.”

From the overall cohort, 33 patients (5%) were analyzed. The median age at treatment initiation was 82 years, and 55% of patients were male. Twenty-two patients (71%) had relevant comorbidities and 30 patients had impaired renal function. Sixty-nine percent of patients were categorized as high- or very-high risk. The most frequent frontline regimens were venetoclax plus obinutzumab (82%; n = 27), bendamustine debunking with ibrutinib plus obinutuzumab (9%; n = 3), venetoclax plus obinutuzumab and ibrutinib (6%; n = 2), and bendamustine with ibrutinib plus ofatumumab (3%; n = 1).

The overall response rate to treatment was 73%, with 36% of patients achieving a complete response. The rates of undetectable measurable residual disease in this subgroup were 73% in peripheral blood and 39% in bone marrow.

Three patients discontinued treatment due to progressive disease, four due to patient decision, and two due to “other” reasons. There were 11 fatalities overall, with five related to adverse events (AEs) and one each due to heart failure, pulmonary embolism, and renal failure. Other causes of death not related to AEs were progressive disease, infection, and respiratory insufficiency. One patient had an unknown cause of death. Nine secondary malignancies occurred in seven patients; the most common malignancy was basal cell carcinoma (44%).

According to time-to-event analyses, the median progression-free survival (PFS) was 49 months. The researchers reported that, in a matched cohort of patients younger than 80 years, median PFS was not yet reached. In the older patient cohort, the four-year OS rate was 68%, compared with 92% in the matched cohort. Median OS and median time-to-next-treatment were not reached.

Based on the average mortality rate in the ≥80 years age

group, the standardized mortality ratio was 0.78 (95% confidence interval 0.39-1.4), with 11 observed deaths versus 14 expected deaths.

"Very old patients treated with targeted agents have a comparable survival to an age- and sex-matched population, suggesting that initiating treatment in elderly and potentially frail patients is beneficial," the authors concluded. "Dedicated studies are warranted for this clinical setting." ■

Source: 2021 ASH Annual Meeting, Abstract #1552

Peripheral Blood Cytopenias Could Represent an Early Marker of Cancer Mortality Risk

Peripheral blood cytopenia is a persistent clinical challenge and, according to findings from the REGARDS trial, it may be associated with a higher risk of cancer-related mortality, particularly in Black patients. These findings suggest that cytopenia may be an early marker of severe disease, reported Diego Adrianzen Herrera, MD, of the Larner College of Medicine at the University of Vermont in Burlington, who presented the findings during the 2021 ASH Annual Meeting.

REGARDS included 30,239 U.S. individuals who were followed with a semiannual phone interview through 2018 for cytopenia and cancer mortality.

The hazard of cytopenia-related cancer mortality was calculated in Cox proportional hazards models: Model 1 adjusted for demographics, Model 2 adjusted for Model 1 plus risk factors for cancer/anemia, and Model 3 adjusted for Model 1 plus socioeconomic factors. Additionally, the researchers assessed differences in the association of cytopenia and cancer death by race.

Of the 19,028 participants who were included in the analysis, 60% were White and 62% were female. There were 1,112 cancer deaths and 3,725 deaths from other causes during the median follow-up period of nine years. Approximately 2% (n = 383) of participants had cytopenia, including 65% (n = 25) of White patients and 35% (n = 113) of Black patients. The prevalence of cytopenia increased by advancing age and was highest in males (56%).

In all multivariate models, cytopenia was significantly associated with increased risk of cancer mortality, including in models adjusted for demographics (hazard ratio [HR] = 1.60), cancer risk factors (HR = 1.67), and socioeconomic variables (HR = 1.58). Additionally, both anemia and macrocytosis were associated with the risk of cancer-related death in all three hazard models.

The 10-year cumulative incidence of cancer-related death was significantly greater in patients with than without baseline cytopenia (13% vs. 6.5%, respectively; $p < 0.01$). In the analysis of race by cytopenia interaction, the HR for cancer mortality was significantly higher in Black patients compared with White patients in Model 1 (2.01 vs. 1.41, respectively; $p = 0.016$), Model 2 (2.12 vs. 1.45; $p = 0.009$), and Model 3 (1.82 vs. 1.44; $p = 0.04$).

Across all models, individual hematologic parameters with higher HR for cancer in Black versus White patients included anemia and macrocytosis. These findings could inform further studies aimed at clarifying racial disparities in cancer death through theorized mechanisms such as clonal hematopoiesis, the authors concluded. ■

Source: 2021 ASH Annual Meeting, Abstract #177

> **"According to findings from the REGARDS trial, peripheral blood cytopenias may be associated with a higher risk of cancer-related mortality, particularly in Black patients."**

Ibrutinib Plus Ianalumab Shows Promising Results in Early-Phase Trial

According to findings from a dose-escalation/expansion trial presented at the 2021 ASH Annual Meeting, adding ianalumab to ibrutinib was well-tolerated, with clinical activity in several patients with chronic lymphocytic leukemia (CLL). Many patients achieved undetectable measurable residual disease (MRD) status in peripheral blood and bone marrow, allowing six participants to discontinue ibrutinib therapy for an extended period.

The B-cell activating factor receptor (BAFF-R) enhances the survival and regulation of normal and malignant B cells, the investigators explained. Ianalumab is a human monoclonal antibody targeting BAFF-R that targets BAFF-R+ B cells for elimination by antibody-dependent cell-mediated cytotoxicity (ADCC). "In preclinical models, adding [ianalumab] to ibrutinib significantly improved survival and reduced disease burden, suggesting that this combination may augment the anti-leukemia response and allow patients to discontinue ibrutinib," the authors wrote.

The trial enrolled 32 patients with CLL who were undergoing either first- or second-line therapy with ibrutinib and whose disease failed to achieve a complete response (CR) after more than one year of therapy, or who had CLL with a mutation associated with ibrutinib resistance.

Participants received oral ibrutinib 420 mg once daily and ianalumab at 0.3, 1, 3, or 9 mg/kg once every two weeks. In the expansion phase, patients were enrolled into two arms depending on whether ibrutinib resistance mutations were present at baseline. The ianalumab + ibrutinib combination was administered for up to six 28-day cycles. After six cycles, patients with a CR discontinued ianalumab and received ibrutinib for an additional two cycles; all other participants continued ianalumab + ibrutinib for those two cycles. Patients achieving undetectable measurable residual disease (MRD) at cycle nine day one could discontinue ibrutinib at the investigator's discretion.

Of the 32 patients enrolled, 19 completed therapy and four discontinued ianalumab + ibrutinib (primarily due to disease progression). Another four patients remain on ianalumab + ibrutinib and five patients continue to receive ibrutinib.

Twelve patients (38%) experienced grade ≥3 adverse events, the most common of which (occurring in ≥2 patients) were neutrophil count decreased (n = 5), lymphocyte count decreased (n = 2), hypophosphatemia (n = 2), and elevated lipase (n = 2).

The overall response for 21 evaluable patients was 38% CR, 5% CRi, 14% and PR, 24%. Thirteen patients (41%) achieved undetectable MRD in blood, while eight patients (42%) had undetectable MRD in blood and bone marrow at the end of treatment. Among those, six patients were elected to discontinue ibrutinib and remained off-treatment for 0.2 to 26.2 months. These patients were still off therapy at the data cutoff.

"These data provide clinical evidence of the potent anti-leukemia activity of [ianalumab] and the potential to safely discontinue ibrutinib or other BTK inhibitors by [ianalumab] add-on therapy," the authors concluded. ■

Source: 2021 ASH Annual Meeting, Abstract #2631

Evaluating Fixed-Duration Ibrutinib and Venetoclax in Relapsed/Refractory Chronic Lymphocytic Leukemia

A fixed-duration combination of the first-generation Bruton tyrosine kinase (BTK) inhibitor ibrutinib and the first-generation BCL2 inhibitor venetoclax appeared to be a well-tolerated, effective, all-oral regimen for patients with relapsed/refractory chronic lymphocytic leukemia (CLL). Tanya Siddiqi, MD, from City of Hope National Medical Center in Duarte, Calif., presented findings from the phase II trial at the 2021 ASH Annual Meeting. Dr. Siddiqi added that most patients achieved an undetectable measurable residual disease (MRD) in bone marrow.

"[Ibrutinib and venetoclax] are both oral agents that have been shown to work synergistically together with no unexpected toxicities beyond what is already known about each of them," Dr. Siddiqi explained. The combination has proven effective in frontline treatment of CLL, including fixed-duration therapy for 15 cycles which produces high complete remissions (CR) and undetectable MRD rates, as well as high progression-free survival (PFS) and overall survival (OS).

In this study, researchers examined the combination in the relapsed/refractory setting, enrolling 22 patients. The median

number of prior treatments was one (range = 1-3). No patients had prior exposure to a BTK inhibitor or venetoclax,

Treatment consisted of ibrutinib 420 mg as monotherapy for eight weeks, after which venetoclax ramp-up treatment was introduced, then escalated to a full dose of 400 mg daily over five weeks. The combination of ibrutinib and venetoclax was then continued for a total of two years.

Overall, 21 patients initiated venetoclax and 18 patients completed full trial treatment. Three patients discontinued treatment due to Hodgkin transformation, kidney failure, and need for a coronary stent. Five patients interrupted dosing due to toxicity and five patients had dose reductions.

At week 62, the CR rate in the intent-to-treat population of 22 patients was 55%, while the overall response rate was 91%. Two-year rates of PFS and OS were 95% and 100%, respectively. After one year of combination therapy, 13 of 20 (65%) evaluable patients had achieved undetectable MRD in bone marrow.

After two years of follow-up, an additional two patients achieved undetectable MRD in bone marrow, the researchers noted.

Seven patients experienced 11 serious treatment-related adverse events (AEs), including sepsis (n = 3), pneumonia (n = 3), atrial fibrillation (n = 2), and diarrhea, dehydration, and pulmonary embolism (n = 1 each). There were no events of tumor lysis syndromes, the investigators reported. ■

Source: 2021 ASH Annual Meeting, Abstract #3754

> **"[IBRUTINIB AND VENETOCLAX] ARE BOTH ORAL AGENTS THAT HAVE BEEN SHOWN TO WORK SYNERGISTICALLY TOGETHER WITH NO UNEXPECTED TOXICITIES BEYOND WHAT IS ALREADY KNOWN ABOUT EACH OF THEM."**

Evaluating Adoptive Immunotherapy to Prevent Acute GVHD

Adoptive immunotherapy with CD4+/CD25/+FOXP3+ regulatory T cells (Tregs) and conventional T cells (Tcons) has been used as prevention of graft-versus-host disease (GVHD) in patients undergoing allogeneic hematopoietic cell transplantation (alloHCT). In a poster presented at the 2021 ASH Annual Meeting by Samanta Bonato, MD, from the University of Perugia in Italy, researchers evaluated clinical and histological characteristics of acute GVHD and their impact on outcomes in patients who received Treg/Tcon haploidentical alloHCT.

The investigators retrieved data from patients who underwent Treg/Tcon haploidentical alloHCT at Perugia University Hospital and were evaluable for acute GVHD from January 2015 until June 2021. They also analyzed histological features and lymphoid infiltration by immunohistochemistry in gut samples of patients who received diagnostic colonscopy and biopsy for gastrointestinal symptoms.

The study included 105 patients who had engraftment after Treg/Tcon haploidentical alloHCT. Mean age at alloHCT was 48 years, and acute leukemia was the most frequent diagnosis (n = 78/105). Twenty-seven patients (26%) had active disease at the time of transplantation.

Thirty-one patients (29%) developed grade II-IV aGVHD: four with grade II, 23 with grade III, and four with grade IV. Nearly all patients (90%) presented gut involvement, while skin was involved in 64% of them and liver in 35%.

"To explain why gut symptoms such as diarrhea and abdominal pain were more frequently present than symptoms of skin or liver involvement, we evaluated 40 histological samples from 34 patients who received colonoscopy for suspected aGVHD," the authors explained. Nearly two-thirds of these patients (n = 22) received a clinical diagnosis of aGVHD and pharmacologic immune suppression was promptly initiated. However, clinical diagnosis did not always match histological findings. Biopsies were suggestive of aGVHD in 20 of the 22 patients who required treatment, as well as in eight of the 12 patients who did not.

The investigators found no difference in median CD3+ cell infiltration among patients who did not need immune-suppressive treatments and patients with aGVHD. However, FOXP3+ Tregs preferentially infiltrated gut mucosa of patients

who resolved clinical symptoms with no need of immune-suppressive treatments. "This observation suggested Treg defective homing to gut mucosa of aGVHD patients," they reported. "Indeed, we found infused Tregs expressed lower levels of gut homing receptor α4β7 in comparison with Tcons."

While most patients had severe aGVHD at diagnosis, disease resolved in most patients (71%), and immune-suppressive therapy could be completely withdrawn after a relatively short course (median of 98 days).

The researchers also reported that an aGVHD diagnosis did not lead to higher incidence of non-relapse mortality, relapse, or chronic GVHD compared with controls who never developed GVHD.

Overall, they concluded that Treg/Tcon haploidentical alloHCT is associated with good rates of chronic GVHD- and leukemia-free survival in patients with high-risk leukemia. "Strategies that enhance Treg homing in the gut (e.g., low-dose IL-2) may help reduce aGVHD after Treg/Tcon haploidentical alloHCT," they wrote. ■

Source: 2021 ASH Annual Meeting, Abstract #2885

MRD-Guided Ibrutinib Combination Successful in Relapsed/Refractory Chronic Lymphocytic Leukemia

Research presented at the 2021 ASH Annual Meeting suggests that patients with relapsed/refractory chronic lymphocytic leukemia (CLL) suggests that measurable residual disease (MRD)–guided, time-limited treatment with ibrutinib and venetoclax demonstrates a favorable benefit-risk profile. This is according to a study by Carsten Utoft Niemann, MD, PhD, from Copenhagen University Hospital in Denmark, and colleagues.

The researchers added that no new safety signals were detected in the trial, and no patients had disease progression after treatment cessation. Patients who became MRD-positive were able to successfully reinitiate therapy, the authors added, "thus proving MRD-guided cessation and re-initiation of targeted therapy feasible in CLL."

Dr. Niemann and colleagues evaluated progression-free survival (PFS) in 225 patients with relapsed/refractory CLL at 12 months after MRD-guided treatment cessation of venetoclax plus ibrutinib treatment, with the option to reinitiate the combination on MRD reappearance.

Patients who were BTK inhibitor-naïve received ibrutinib lead-in at a dose of 420 mg daily for two 28-day cycles. Venetoclax ramp-up was initiated during cycle 3, reaching 400 mg daily at cycle 4 with continued venetoclax plus ibrutinib during cycles 4 through 15. At cycle 15, 36% of patients achieved undetectable MRD in peripheral blood or bone marrow. The overall response rate was 86%, which included a rate of complete response with incomplete hematologic recovery of 64%.

Next, patients reaching at least partial remission (PR) and undetectable MRD at day 15 of cycle 15 were randomized 1:2 to receive ibrutinib maintenance (arm A) or treatment cessation (arm B). Patients in arm B who did not achieve undetectable MRD continued ibrutinib maintenance without randomization.

The researchers concluded that the primary endpoint of the trial was met, with 98% of patients in arm B achieving PFS at 12 months after randomization. They added that no difference in undetectable MRD at cycle 15 was seen between TP53 aberrated/wild-type patients or IGHV unmutated/mutated patients.

The most frequent adverse event was infections (30%). Atrial fibrillation was reported for 29 patients (13%) during the first 15 cycles, while no patients under observation in arm B experienced atrial fibrillation. ■

Source: 2021 ASH Annual Meeting, Abstract #69

> "THE TRIAL'S PRIMARY ENDPOINT WAS MET, WITH 98% OF PATIENTS ACHIEVING PROGRESSION-FREE SURVIVAL AT 12 MONTHS AFTER RANDOMIZATION."

Combination of Venetoclax, Obinutuzumab, and Atezolizumab Shows Promise in Richter's Transformation

According to results presented at the 2021 American Society of Hematology Annual Meeting, patients with previously untreated Richter's transformation (RT) had high rates of remission with venetoclax, obinutuzumab, and atezolizumab.

In previous studies, the BCL2 inhibitor venetoclax and CD20 monoclonal antibody obinutuzumab have shown clinical activity in patients with diffuse large B-cell lymphoma (DLBCL) and RT. PD-L1 checkpoint inhibitor atezolizumab has been approved by the FDA for the treatment of melanoma, lung cancer, and other solid tumors.

From March 2020 to June 2021, researchers led by Nitin Jain, MD, of MD Anderson Cancer Center, enrolled eight patients with DLBCL RT in a phase II trial. Eligible patients with either previously untreated (n = 7) or relapsed/refractory (n = 1) RT were at least 18 years of age, had adequate organ function, and had not undergone prior treatment with venetoclax.

The median age of patients in the study was 70 years (range = 52-80). Patients had previously been treated for CLL with ibrutinib (n = 4), chlorambucil plus obinutuzumab followed by acalabrutinib (n = 1), bendamustine-rituximab (n = 1). All six patients for whom CLL IGHV mutation status was available were IGHV-mutated. Three patients had complex karyotype, three had a *TPS53* mutation, and two had a *NOTCH1* mutation. CLL FISH panel found the following:

- del17p (n = 4)
- del11q (n = 1)
- trisomy 12 (n = 1)
- normal (n = 1)

Treatment consisted of the following:

- intravenous (IV) obinutuzumab: 100 mg on cycle 1 day 1, 900 mg on cycle 1 day 2, 1,000 mg on cycle 1 days 8 and 15, 1,000 mg on day 1 of cycles 2-9
- IV atezolizumab: 1,680 mg (split over 2 days) on cycle 1 days 3-4 and days 1-2 of cycles 2-9
- venetoclax 20 mg daily at the start of cycle 2 with weekly dose escalation to a target dose of 800 mg daily until the end of cycle 26

Responses were evaluated using PET imaging and bone marrow aspirate/biopsy with measurable residual disease (MRD) assessment at the end of cycles 1, 4, 9, and 26. All seven patients achieved a response, including five complete metabolic responses and two partial metabolic responses. All but one of the responses occurred after the introduction of venetoclax in cycle 2. The remaining patient achieved complete metabolic response and bone marrow undetectable MRD after cycle 1.

> **"ALTHOUGH THIS STUDY IS LIMITED BY ITS SMALL SAMPLE SIZE, THESE RESULTS ARE ENCOURAGING IN RELATION TO COMBINED IBRUTINIB PLUS NIVOLUMAB IN THIS SETTING."**

Three patients underwent allogeneic stem cell transplant (alloSCT) in complete metabolic remission after 4.1, 4.2, and 6.6 months. Bone marrow undetectable MRD remission was also achieved in these three patients. One of the three has since relapsed and is currently receiving salvage therapy, the authors noted.

One patient who achieved partial metabolic remission relapsed prior to a planned alloSCT in cycle 8, but after treatment with a non-covalent BTK inhibitor, is now in remission, they added. Three patients continue to receive treatment on the trial in cycle 2, cycle 5, and cycle 12.

The patient with relapsed/refractory RT was a 58-year-old male with previously untreated CLL (unmutated IGHV, del17p, *TPS53* mutation, and *NOTCH1* mutation). Prior to enrollment in the trial, this patient received R-CHOP for three cycles but had no response.

No deaths were observed during follow-up. One patient developed pancreatitis associated with checkpoint inhibitor treatment and diabetes mellitus. Another patient required the venetoclax dose to be reduced to 400 mg daily.

Although this study is limited by its small sample size, "these results are encouraging in relation to combined ibrutinib plus nivolumab in previously untreated RT," Dr. Jain wrote. ■

Source: 2021 ASH Annual Meeting, Abstract #1550

Below is a List of Resources Available to **YOU.**

Scientific Resources, Medical Inquiries, and Research Support

- Pharmacyclics provides our medical community with timely, comprehensive medical information as well as data updates from national and regional conferences on approved Pharmacyclics products and relevant disease states.
- We assist current clinical research sites for company-sponsored trials with continued education of the study team on the study design, protocol activities, and data read-outs.

Partnerships for Education

We provide non-promotional educational programs on approved Pharmacyclics products and supported disease states, including:

- Disease state education
- Product clinical overview, including efficacy, safety, and adverse event management
- Clinical trial design overview
- Medical conference data reviews

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