Survey reveals special impact of COVID-19 on patients with rare disorders

New agents boost survival – and complexity – in chronic lymphocytic leukemia

Targeted therapies may alter the landscape of MCL treatment

Will CAR T push beyond lymphoma? There’s no guarantee
VENCLEXTA + GAZYVA® (obinutuzumab) DELIVERS CHEMO-FREE TREATMENT WITH THE STRENGTH* TO STOP† AFTER 12 MONTHS IN 1L CLL¹

*CLL14 was a randomized (1:1), multicenter, actively controlled, open-label phase 3 study that evaluated the efficacy and safety of VEN+G versus GCB for previously untreated CLL in 432 patients with coexisting medical conditions (total Cumulative Illness Rating Scale [CIRS] score >6 or creatinine clearance <70 mL/min). The primary endpoint was IRC-assessed PFS. VEN+G significantly reduced the risk of death or progression by 67% vs GAZYVA + chlorambucil (HR=0.33, 95% CI: 0.22–0.51 [P<0.0001]). After a median follow-up of 28 months (range: 0.1–36 months), median PFS was not reached in either arm.

†The VEN+G regimen is designed to be completed after 12 months (twelve 28-day treatment cycles): GAZYVA is administered in Cycles 1–6, and VENCLEXTA is taken orally 400 mg/day from Cycle 3, Day 1, after the first cycle of GAZYVA and the 5-week VENCLEXTA dose ramp-up.

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Indication and Important Safety Information

Indication

▪ VENCLEXTA is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).

Important Safety Information

Contraindication

▪ Concomitant use of VENCLEXTA with strong CYP3A inhibitors at initiation and during ramp-up phase is contraindicated in patients with CLL/SLL due to the potential for increased risk of tumor lysis syndrome (TLS).

Tumor Lysis Syndrome

▪ Tumor lysis syndrome, including fatal events and renal failure requiring dialysis, has occurred in patients with high tumor burden when treated with VENCLEXTA.

▪ In patients with CLL who followed the current (5 week) dose ramp-up and the TLS prophylaxis and monitoring measures, the rate of TLS was 2% in the VENCLEXTA CLL monotherapy studies. The rate of TLS remained consistent with VENCLEXTA in combination with obinutuzumab or rituximab. With a 2- to 3-week dose ramp-up and higher starting dose in patients with CLL/SLL, the TLS rate was 13% and included deaths and renal failure.

▪ VENCLEXTA poses a risk for TLS at initiation and during the ramp-up phase. Changes in blood chemistries consistent with TLS that require prompt management can occur as early as 6 to 8 hours following the first dose of VENCLEXTA and at each dose increase.

▪ Patients should be assessed for TLS risk, including evaluation of tumor burden and comorbidities, and should receive appropriate prophylaxis for TLS, including hydration and anti-hyperuricemic. Reduced renal function further increases the risk. Monitor blood chemistries and manage abnormalities promptly. Interrupt dosing if needed. Employ more intensive measures (IV hydration, frequent monitoring, hospitalization) as overall risk increases.

▪ Concomitant use of VENCLEXTA with P-gp inhibitors or strong or moderate CYP3A inhibitors may increase the risk of TLS at initiation and during the ramp-up phase, and requires dose adjustment due to increases in VENCLEXTA exposure.

Neutropenia

▪ In patients with CLL, Grade 3 or 4 neutropenia developed in 63% to 64% of patients and Grade 4 neutropenia developed in 31% to 33% of patients treated with VENCLEXTA in combination and monotherapy studies. Febrile neutropenia occurred in 4% to 6% of patients treated with VENCLEXTA in combination and monotherapy studies. Consider supportive measures including antimicrobials for signs of infection and use of growth factors (e.g., G-CSF).

Infections

▪ Fatal and serious infections such as pneumonia and sepsis have occurred in patients treated with VENCLEXTA. Monitor patients closely for signs and symptoms of infection and treat promptly. Withhold VENCLEXTA for Grade 3 and higher infection.

Immunization

▪ Do not administer live attenuated vaccines prior to, during, or after treatment with VENCLEXTA until B-cell recovery occurs. Advise patients that vaccinations may be less effective.

Embryo-Fetal Toxicity

▪ VENCLEXTA may cause embryo-fetal harm when administered to a pregnant woman. Advise females of reproductive potential to avoid pregnancy during treatment.

Increased Mortality in Patients with Multiple Myeloma when VENCLEXTA is Added to Bortezomib and Dexamethasone

▪ In a randomized trial (BELLINI; NCT02755597) in patients with relapsed or refractory multiple myeloma, the addition of VENCLEXTA to bortezomib plus dexamethasone, a use for which VENCLEXTA is not indicated, resulted in increased mortality. Treatment of patients with multiple myeloma with VENCLEXTA in combination with bortezomib plus dexamethasone is not recommended outside of controlled clinical trials.

Distributed and marketed by AbbVie Inc., 1 North Waukegan Road, North Chicago, IL 60064 Marketed by Genentech USA, Inc., 1 DNA Way, South San Francisco, CA 94080-4990 ©2020 AbbVie Inc. and Genentech USA, Inc.
Concomitant use of VENCLEXTA with P-gp inhibitors or strong or moderate CYP3A inhibitors at initiation due to the potential for increased risk of tumor lysis syndrome (TLS). Dialysis, has occurred in patients with high tumor burden when treated overall risk increases.

The rate of TLS remained increases in VENCLEXTA exposure. Monitor blood chemistries and manage TLS, including hydration and anti-hyperuricemics. Reduced renal function burden and comorbidities, and should receive appropriate prophylaxis for dose of VENCLEXTA and at each dose increase.

Phase. Changes in blood chemistries consistent with TLS that require

In patients with CLL, Grade 3 or 4 neutropenia developed in 63% to 64% myeloma with VENCLEXTA in combination with bortezomib plus dexamethasone, a use for which VENCLEXTA is not indicated, resulted in increased mortality. Treatment of patients with multiple myeloma with VENCLEXTA in combination and monotherapy patients treated with VENCLEXTA in combination and monotherapy

Avoid concomitant use of strong or moderate CYP3A inducers.

Avoid concomitant use of VENCLEXTA with a P-gp substrate. If concomitant use is unavoidable, separate dosing of the P-gp substrate at least 6 hours before VENCLEXTA.

Monitor international normalized ratio (INR) closely in patients receiving warfarin.

Adverse Reactions

In patients with CLL receiving combination therapy with obinutuzumab, serious adverse reactions were most often due to febrile neutropenia and pneumonia (5% each). The most common adverse reactions (>20%) of any grade were neutropenia (60%), diarrhea (28%), and fatigue (21%).

In patients with CLL receiving combination therapy with rituximab, the most frequent serious adverse reaction (≥2%) was pneumonia (9%). The most common adverse reactions (≥20%) of any grade were neutropenia (65%), diarrhea (40%), upper respiratory tract infection (39%), fatigue (22%), and nausea (21%).

In patients with CLL/SLL receiving monotherapy, the most frequent serious adverse reactions (≥5%) were pneumonia (9%), febrile neutropenia (5%), and sepsis (5%). The most common adverse reactions (≥20%) of any grade were neutropenia (50%), diarrhea (43%), nausea (42%), upper respiratory tract infection (36%), anemia (33%), fatigue (32%), thrombocytopenia (29%), musculoskeletal pain (29%), edema (22%), and cough (22%).

Drug Interactions

Concomitant use with a P-gp inhibitor or a strong or moderate CYP3A inhibitor increases VENCLEXTA exposure, which may increase VENCLEXTA toxicities, including the risk of TLS. Adjust VENCLEXTA dosage and closely monitor patients for signs of VENCLEXTA toxicities. If a P-gp inhibitor is used, it is recommended that VENCLEXTA is dosed 400 mg/day from Cycle 3, Day 1, after the first cycle of GAZYVA and the 5-week VENCLEXTA dose ramp-up.

Avoid concomitant use of strong or moderate CYP3A inducers.

Avoid concomitant use of VENCLEXTA with a P-gp substrate. If concomitant use is unavoidable, separate dosing of the P-gp substrate at least 6 hours before VENCLEXTA.

Monitor international normalized ratio (INR) closely in patients receiving warfarin.

Lactation

Advise nursing women to discontinue breastfeeding during treatment with VENCLEXTA.

Females and Males of Reproductive Potential

Advise females of reproductive potential to use effective contraception during treatment with VENCLEXTA and for at least 30 days after the last dose.

Based on findings in animals, male fertility may be compromised by treatment with VENCLEXTA.

Hepatic Impairment

Reduce the dose of VENCLEXTA for patients with severe hepatic impairment (Child-Pugh C); monitor these patients more closely for signs of toxicity. No dose adjustment is recommended for patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment.

Please see Brief Summary of full Prescribing Information on the following pages.

INDICATIONS AND USAGE

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

VENCLEXTA is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).

Acute Myeloid Leukemia

VENCLEXTA is indicated in combination with azacitidine, or decitabine, as a low-dose cytarabine for the treatment of newly-diagnosed acute myeloid leukemia in patients who are age 75 years or older who also have comorbidities that preclude use of intensive induction chemotherapy.

The use of VENCLEXTA in combination with azacitidine or decitabine as a low-dose cytarabine is not indicated in patients who are 75 years of age or who have comorbidities that preclude use of intensive induction chemotherapy.

CONTRAINDICATIONS

Contraindication of using VENCLEXTA with strong CYP3A inhibitors at initiation and during the ramp-up phase is contraindicated in patients with CLL/SLL due to the potential for increased risk of tumor lysis syndrome

WARNINGS AND PRECAUTIONS

Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) was observed in patients with CLL/SLL, including those without tumor burden. Patients with high tumor burden may be at increased risk of TLS. Stopping or reducing VENCLEXTA dose may be necessary to reduce the risk of TLS. Monitor patients for TLS and administer appropriate treatments.

Embryo-Fetal Toxicity

Zoledronic acid (2 mg to 4 mg per 24 hours) during pregnancy or if the patient becomes pregnant while taking VENCLEXTA may cause embryo-fetal harm when administered to a pregnant woman. 

Embryo-Fetal Toxicity

Zoledronic acid is an inhibitor of bone resorption and bone turnover and at higher doses may cause embryo-fetal harm when administered to a pregnant woman. 

Contraindicated in pregnancy and breastfeeding.

Neutropenia

Neutropenia was the most common adverse reaction observed with VENCLEXTA. Neutropenia occurred in 82% of patients in phase 1 trials and 62% of patients in phase 3 trials. Neutropenia occurred in 56% of patients treated with VENCLEXTA in combination with obinutuzumab or chlorambucil. Neutropenia continued in 36%, restarted in 12%, and increased in 3% of patients. Neutropenia was more frequent in patients who received VENCLEXTA in combination with obinutuzumab or chlorambucil than in patients who received VENCLEXTA alone. 

In the VEN+G arm, neutropenia led to dose interruption of VENCLEXTA in 41% of patients, dose reduction in 21%, and dose interruption in 21%. 

Table 1 describes adverse reactions and laboratory abnormalities identified in the CLL14 trial, respectively.

Table 1. Common (≥10%) Adverse Reactions in Patients Treated with Ven-G

<table>
<thead>
<tr>
<th>Body System</th>
<th>All Grades</th>
<th>Grade 3 or 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>83%</td>
<td>63%</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>87%</td>
<td>57%</td>
</tr>
<tr>
<td>Anemia</td>
<td>17%</td>
<td>8%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>22%</td>
<td>2%</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>22%</td>
<td>2%</td>
</tr>
<tr>
<td>Anemia</td>
<td>17%</td>
<td>8%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>22%</td>
<td>2%</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>22%</td>
<td>2%</td>
</tr>
<tr>
<td>Anemia</td>
<td>17%</td>
<td>8%</td>
</tr>
</tbody>
</table>

Table 2. New or Worsening Clinically Important Laboratory Abnormalities Occurring ≥10% in Patients Treated with VENCLEXTA

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukopenia</td>
<td>89%</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>87%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>90%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>93%</td>
</tr>
<tr>
<td>Anemia</td>
<td>53%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>80%</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>80%</td>
</tr>
<tr>
<td>Anemia</td>
<td>53%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>80%</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>80%</td>
</tr>
<tr>
<td>Anemia</td>
<td>53%</td>
</tr>
</tbody>
</table>

INCREASED MORTALITY IN PATIENTS WITH MULTIPLE MYELOMA WHEN VENCLEXTA IS USED IN COMBINATION WITH BORTezOMIB AND DEXAMETHASONE

In a randomized trial (BREVITY; NCT02275535) in patients with relapsed or refractory multiple myeloma, the addition of VENCLEXTA to bortezomib plus dexamethasone, a use for which VENCLEXTA is not indicated, resulted in increased mortality. Treatment of patients with multiple myeloma with VENCLEXTA in combination with bortezomib plus dexamethasone is not recommended outside of controlled clinical trials.

ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed in greater detail in other sections of the labeling:

- Tumor lysis syndrome (see Warnings and Precautions)
- Neutropenia (see Warnings and Precautions)
- Infections (see Warnings and Precautions)
- Death (see Warnings and Precautions)

Clinical Trials

Because clinical trials are conducted under widely variable conditions, adverse event rates observed in clinical trials of a drug cannot be directly

compared with rates of clinical trials of another drug and may not reflect the rates observed in practice.

Table 3. Common (≥10%) Adverse Reactions in Patients Treated with Ven-R

<table>
<thead>
<tr>
<th>Body System</th>
<th>All Grades</th>
<th>Grade 3 or 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>65%</td>
<td>62%</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>65%</td>
<td>62%</td>
</tr>
<tr>
<td>Anemia</td>
<td>16%</td>
<td>11%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>22%</td>
<td>2%</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>22%</td>
<td>2%</td>
</tr>
<tr>
<td>Anemia</td>
<td>17%</td>
<td>8%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>22%</td>
<td>2%</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>22%</td>
<td>2%</td>
</tr>
<tr>
<td>Anemia</td>
<td>17%</td>
<td>8%</td>
</tr>
</tbody>
</table>

Table 4. New or Worsening Clinically Important Laboratory Abnormalities Occurring ≥10% in Patients Treated with Venclexta

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukopenia</td>
<td>89%</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>87%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>90%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>93%</td>
</tr>
<tr>
<td>Anemia</td>
<td>53%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>80%</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>80%</td>
</tr>
<tr>
<td>Anemia</td>
<td>53%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>80%</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>80%</td>
</tr>
<tr>
<td>Anemia</td>
<td>53%</td>
</tr>
</tbody>
</table>

ADVERSE DRUG INTERACTIONS

Concomitant use of VENCLEXTA with P-gp inhibitors or strong or moderate CYP3A inhibitors may increase venetoclax exposure, which may increase the risk of tumor lysis syndrome.

Metabolism and nutrition disorder:

Metabolism and nutrition disorder:

P-gp inhibitors: In patients treated with VENCLEXTA in combination and monotherapy studies (see Drug Interactions), CYP3A inhibitors increases venetoclax exposure, may increase the risk of TLS and during ramp-up phase and require VENCLEXTA dose adjustment (see Drug Interactions).
Grade 4 laboratory abnormalities developing in ≥2% of patients treated with VENCLEXTA included neutropenia (33%), lymphopenia (16%), leukopenia (16%), thrombocytopenia (6%), neutropenia (4%), hypocalcemia (4%), hypophosphatemia (2%), and hyperuricemia (2%).

Tumor Lysis Syndrome

Tumor lysis syndrome is an important identified risk when initiating VENCLEXTA. Important Adverse Reactions

Serious adverse reactions were reported in 85% of patients. The most frequent serious adverse reactions (≥5%) were febrile neutropenia, sepsis (excluding fungal), pneumonia (excluding fungal), diarrhea, fatigue, coagulopathy, and localized infection. One (6%) fatal adverse drug reaction of bacteremia occurred within 30 days of starting treatment.

Table 6. New or Worsening Laboratory Abnormalities with VENCLEXTA

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>VENCLEXTA (N = 302)</th>
<th>Grade ≥3</th>
<th>Grade ≥4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic</td>
<td></td>
<td>All Grades</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>74</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>55</td>
<td>10</td>
<td>13</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>36</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>36</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>40</td>
<td>12</td>
<td>5</td>
</tr>
</tbody>
</table>

Adverse reactions graded using NCI Common Terminology Criteria for Adverse Events version 4.0. Includes multiple adverse reaction terms.

Table 6 describes common laboratory abnormalities reported throughout treatment that were new or worsening from baseline. The most common (≥5%) Grade 4 laboratory abnormalities were hematologic laboratory abnormalities, including neutropenia (33%), leukopenia (16%), lymphopenia (15%), and thrombocytopenia (9%).
The most frequent adverse reactions (≥2%) were thrombocytopenia, neutropenia, and febrile neutropenia. Dosage reductions due to adverse reactions occurred in 8% of patients. Dosage interruptions due to adverse reactions occurred in 52% of patients. Reported in ≥40% (Any Grade) or ≥10% (Grade 3 or 4) of Patients with AML Treated with VENCLEXTA in Combination with Low-Dose Cytarabine

Table 10. New or Worsening Laboratory Abnormalities with VENCLEXTA

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>All Grades</th>
<th>Grade 3 or 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyponatremia</td>
<td>49 (10)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>58 (9)</td>
<td>3 (0)</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>52 (7)</td>
<td>4 (0)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>100 (28)</td>
<td>100 (28)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>100 (28)</td>
<td>100 (28)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>96 (9)</td>
<td>96 (9)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>90 (3)</td>
<td>66 (2)</td>
</tr>
<tr>
<td>Anemia</td>
<td>61 (1)</td>
<td>59 (1)</td>
</tr>
<tr>
<td>Chemosis</td>
<td>65 (0)</td>
<td>60 (0)</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>95 (0)</td>
<td>8 (0)</td>
</tr>
<tr>
<td>Hematuria</td>
<td>79 (0)</td>
<td>16 (0)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>62 (1)</td>
<td>11 (0)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>57 (0)</td>
<td>3 (0)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>59 (0)</td>
<td>9 (0)</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>51 (0)</td>
<td>21 (0)</td>
</tr>
<tr>
<td>Hypoproteinemia</td>
<td>46 (0)</td>
<td>46 (0)</td>
</tr>
<tr>
<td>Blood creatinine increased</td>
<td>46 (0)</td>
<td>46 (0)</td>
</tr>
<tr>
<td>Blood lactate decreased</td>
<td>41 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Adverse reactions in patients with newly-diagnosed AML treated with VENCLEXTA in combination with Azacitidine or Decitabine

The most frequent adverse reactions (≥2%) were thrombocytopenia, neutropenia, and febrile neutropenia (excluding fungal). Dosage reductions due to adverse reactions occurred in 52% of patients. Dosage interruptions due to adverse reactions occurred in 52% of patients. Reported in ≥40% (Any Grade) or ≥10% (Grade 3 or 4) of Patients with AML Treated with VENCLEXTA in Combination with Low-Dose Cytarabine

Table 9. Adverse Reactions Reported in ≥30% (Any Grade) or ≥15% (Grade 3 or 4) of Patients with AML Treated with VENCLEXTA in Combination with Low-Dose Cytarabine

<table>
<thead>
<tr>
<th>Adverse Reaction by Body System</th>
<th>VENCLEXTA (N = 61)</th>
<th>VENCLEXTA in Combination with Azacitidine (N = 47)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hematology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>100 (28)</td>
<td>100 (28)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>100 (28)</td>
<td>100 (28)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>96 (9)</td>
<td>96 (9)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>90 (3)</td>
<td>66 (2)</td>
</tr>
<tr>
<td>Anemia</td>
<td>61 (1)</td>
<td>59 (1)</td>
</tr>
<tr>
<td>Chemosis</td>
<td>65 (0)</td>
<td>60 (0)</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>95 (0)</td>
<td>8 (0)</td>
</tr>
<tr>
<td>Hematuria</td>
<td>79 (0)</td>
<td>16 (0)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>62 (1)</td>
<td>11 (0)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>57 (0)</td>
<td>3 (0)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>59 (0)</td>
<td>9 (0)</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>51 (0)</td>
<td>21 (0)</td>
</tr>
<tr>
<td>Hypoproteinemia</td>
<td>46 (0)</td>
<td>46 (0)</td>
</tr>
<tr>
<td>Blood creatinine increased</td>
<td>46 (0)</td>
<td>46 (0)</td>
</tr>
<tr>
<td>Blood lactate decreased</td>
<td>41 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>64 (2)</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>44 (3)</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>33 (5)</td>
<td></td>
</tr>
<tr>
<td><strong>Respiratory disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>26 (5)</td>
<td></td>
</tr>
<tr>
<td><strong>Infections and infestations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td>20 (18)</td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>18 (16)</td>
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<td>Device-related infection</td>
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<tr>
<td>Uremia-related infection</td>
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<tr>
<td><strong>Vascular disorders</strong></td>
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<tr>
<td>Hypertension</td>
<td>49 (15)</td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>21 (7)</td>
<td></td>
</tr>
<tr>
<td><strong>Adverse reactions graded using CIOMS Common Terminology Criteria for Adverse Events 4.0</strong></td>
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EDITORS’ NOTE

Rare cancers, though individually rare by definition, impose a tremendous burden on adult and pediatric patient populations, especially when considering hematological cancers. In this Rare Diseases Report: Cancers, we bring you the latest information on new and ongoing developments in the treatment of some of these cancers through interviews with frontline researchers in the field.

We hope you enjoy the issue.

– Jennifer Smith, Editor, Oncology Practice

– Mark S. Lesney, Managing Editor, Hematology News

A NOTE FROM NORD

Entering a new era in rare cancer treatment

In last year’s version of Rare Diseases: Cancers, we wrote about rallying public awareness of rare cancers through the first-ever “Rare Cancer Day” organized by the National Organization for Rare Disorders (NORD) and the NORD Rare Cancer Coalition. The coalition is an alliance of organizations representing specific rare cancer communities.

Rare Cancer Day was very successful and has now become an annual event (on September 30 each year) to promote awareness of rare cancers and support for clinicians, researchers, patients, and caregivers.

For Rare Cancer Day 2020, NORD and the Rare Cancer Coalition featured the potential value of genomic testing in helping patients find targeted therapies and personalized treatment options. Through social media and online educational resources, Rare Cancer Day has reached millions of people and raised critical awareness of the need for greater research funding, effective treatments, access to diagnostic testing, and services for patients and families coping with the feelings of fear and isolation that often accompany a rare cancer diagnosis.

In addition to awareness activities, the Rare Cancer Coalition is also committed to developing educational resources for medical professionals, patients, and caregivers. For instance, we are currently making final preparations for a rare cancer track at the 2020 NORD Rare Diseases and Orphan Products Breakthrough Summit.

The NORD Summit is the largest annual multistakeholder event for the rare disease community, and the rare cancer track draws together participants from government (primarily the National Institutes of Health and the Food and Drug Administration), patient organizations, industry, and academia.

This year, we will focus on two topics of particular timeliness in rare oncology: increasing application of patient-reported data and the current status and future directions of precision oncology.

The members of the Rare Cancer Coalition also work collaboratively for capacity-building and sharing of knowledge and resources. Our goal is for each member of the coalition to provide the best possible service to its particular rare cancer community. We also work with NORD on various initiatives such as webinars, CME resources, patient registries and natural history studies, and regional patient/family conferences.

We welcome new members, and we encourage anyone involved in a rare cancer advocacy or awareness organization to contact us to learn about opportunities to join the coalition to promote and support rare cancer research, awareness, and education.

—Jim Palma
Executive Director,
TargetCancer Foundation
Rare Cancer Coalition Co-Chair

—John Hopper
President,
The Fibrolamellar Cancer Foundation
Rare Cancer Coalition Co-Chair
It seems naive now, but in the early days of the COVID-19 crisis, there was a debate among public health experts and media about whether to label it an “epidemic,” which affects only people within a specific population, community, or region, or a “pandemic,” an epidemic that spans continents and spreads rapidly throughout the world.

Today, all reasonable doubts about the virulence and transmissibility of SARS-CoV-2, the virus that causes COVID-19, have been erased, along with the lives of more than 202,000 people in the United States and more than 1 million people worldwide as of this writing.

Among the myriad pernicious effects of the COVID-19 pandemic – social disruptions, financial chaos, the politicization of public health measures – the effects on health care have been especially severe, and perhaps nowhere more challenging than for patients with rare cancers and the clinicians who care for them.

The National Organization for Rare Disorders (NORD) has documented the barriers to care caused by the pandemic as well as the unique concerns of patients with rare diseases in a NORD Rare Insights report.1

NORD had previously published survey results revealing that people with rare diseases and their families suffered major disruption in their care and well-being in the early days of the pandemic.

The current report details the results of a second survey conducted in June 2020, including responses from 833 people, primarily patients with rare diseases but also their family members and advocates.

“These unprecedented times have upset the balance of a health care system that already did not work in favor of most people with rare diseases,” the report says. “Patients and families typically face an uphill battle trying to find a diagnosis; often encounter a lack of treatment options; experience the hope and precariousness of participating in research or clinical trials; and travel extensively to be seen by disease-specific experts – all in the hope of gaining some relief or chance at improved well-being.”

In addition to finding that 92% of patients with rare diseases are still adversely affected by the pandemic, the report’s authors found that:

• More than three-quarters of respondents (79%) reported canceled medical appointments.
• About one-third (32%) said they had challenges accessing medical care and treatment.
• Fourteen percent reported difficulties getting access to medical supplies, and two-thirds of those respondents (68%) said they had trouble acquiring personal protective equipment (PPE), which is especially important for patients with immune disorders and those who are taking immunosuppressant therapies.
• More than a third of respondents (37%) said their households had been affected by a lack of income, and 27% reported job losses. Among those who lost jobs, 9% also lost health insurance.

Care delayed, cure denied
For patients with cancer – especially those with rare malignancies, who have few therapeutic options – the stakes are high.

“We’re seeing patients who apparently had curable disease, and they put off surgery, or the centers put off surgery – I don’t know whether to blame the center or the fear of COVID – and now their disease is no longer curable,” said Razelle Kurzrock, MD, distinguished professor of medicine at the University of California, San Diego, and director of the center for personalized cancer therapy and rare tumor clinic at Moores Cancer Center.

Dr. Kurzrock and Dr. O’Neill have no relevant disclosures.
Clinical trials on hold

For many patients with rare aggressive malignancies, an experimental therapy may be the last, best hope, but many potentially practice-changing trials were put on hold at the height of the pandemic.

Coast-to-coast declines

In Boston, an early epicenter of the pandemic, Allison F. O’Neill, MD, clinical director of the solid tumor center at the Dana-Farber Cancer Institute and assistant professor of pediatrics at Harvard Medical School, Boston, and colleagues saw a more than 50% decline in new-patient visits during the height of the surge, as they noted in a recent commentary in the journal Pediatric Blood & Cancer.

“Certainly, our numbers were down substantially at the peak of the COVID-19 shutdown. We have since seen a rebound in the number of cases and patients that have come to our institute as the city and the state have opened up gradually,” Dr. O’Neill said in an interview.

The majority of pediatric patient diagnoses and referrals to Dana-Farber come from primary care pediatricians and family physicians in the community, she noted.

The drop-off in visits during the height of the pandemic appears to have been caused by “a unique overlay of families being somewhat reluctant to go to their primary care pediatricians, primary care pediatricians not holding standard hours, and then ultimately there being fewer patients to present to tertiary care centers for their oncologic care,” she said.

Clinical trials on hold

For many patients with rare aggressive malignancies, an experimental therapy may be the last, best hope, but many potentially practice-changing trials were put on hold at the height of the pandemic.

“I have three patients like that. Now, one could argue that they have underlying aggressive disease and maybe they wouldn’t have been cured in the first place,” she said. “But I would argue that we don’t know that, and it’s a pretty devastating consequence.”

Many patients with cancer are still reluctant to seek care at a hospital, and in the early days of the pandemic, hospitals in COVID-19 epicenters were canceling or rescheduling “nonessential” surgery.

“They said that they were still doing all the essential surgeries, but to me, all cancer surgery is essential,” Dr. Kurzrock said.

Also early on, patients with metastatic disease were delaying vital scans.

“We’ve seen patients who were scanned in January and then didn’t get scanned again until June. These patients really need to be scanned every 2 months or 3 months, but definitely not only every 6 months,” she said.

Many patients may have difficulties assessing the relative risks from COVID-19 compared with the risks for delaying chemotherapy or other life-extending therapy, Dr. Kurzrock said.

“I had several patients call me on the weekend, just terrified because they could no longer go on the clinical trial that they had been hoping for,” Dr. Kurzrock said.

Although many centers said essential trials would continue during the pandemic, the definition of essential is fuzzy at best.

“There are a lot of new drugs out there, and we don’t know whether they are better or worse, and those would be considered nonessential trials. But for individual patients, especially a patient with a rare tumor who doesn’t have many options, if there’s an exciting new drug, even if we don’t have proof that drug works, that can be very important to them,” Dr. Kurzrock said.

At Dana-Farber, however, pediatric clinical trials remained open and continued to enroll patients during the pandemic, Dr. O’Neill said.

“I think what patients and families are feeling most is the inability to travel, because sometimes rare cancers require referral to a large center, and everyone is reluctant to travel, and so access to trials, even if they’re open, may be impacted,” she said.

Not just phoning it in

At least one side effect of the COVID-19 pandemic has been beneficial. One of the biggest changes has been in patient visits, both Dr. Kurzrock and Dr. O’Neill said.

“Patients may come to the clinic from San Diego, from anywhere in the country, and sometimes from anywhere in the world, and I would say that certainly patients who were coming from outside San Diego are now being seen by telehealth visits rather than an in-person visit,” Dr. Kurzrock said.

Many patients who live near her center and could get there without too much trouble also ask for telehealth visits, which represents a major change in practice, she said.

But she adds that there are both negative and positive aspects to the shift toward telehealth.

“Telehealth seems to have sprung up spontaneously. The university got it up and running in just a few days. It’s not running perfectly, to be frank, but it’s pretty good considering how fast it was put in place,” Dr. Kurzrock said.

Although she prefers in-person visits, telehealth or telemedicine “with a few tweaks” can be a positive change, because it allows geographically remote patients to have the benefits of visits and consultations with experts who can have in-depth discussions, review scans, and provide advice about how to stay well and stay safe.

Dr. Kurzrock emphasized that a face-to-face visit on a smartphone won’t cut it. Telemedicine visits should be performed with both parties having devices with reasonably large screens and stable and secure conferencing software, as well as digital access to vital signs for the clinician.
Dr. O’Neill agreed that, in the absence of in-person visits, telemedicine has made a substantial difference.

“It will never replace a physical exam,” she emphasized, but she also pointed out that oncologists can obtain patient records remotely, share them with the tumor board, and connect with families to have detailed discussions regarding first-line therapies, obtaining second opinions, and other vital aspects of cancer care.

“We’ve noticed such a substantial increase in our telemedicine visits that if you look at the decrease in in-person visits, they’re more than accounted for by the increase in telemedicine visits, so, overall, our visits are actually up,” she said.

Dr. O’Neill pointed to one drawback of telemedicine not often mentioned in media reports: namely, that clinicians are not licensed in all states, leading to questions about liability, insurance coverage for remote visits, and other potential legal and logistical roadblocks.

The NORD report notes that “telemedicine has emerged as a bright spot for many people with rare diseases as a way to safely and confidently access medical care without risking exposure to COVID-19.”

The report shows a clear rise in the uptake and acceptance of telemedicine, with the proportion of respondents who reported being offered telemedicine visits at 83%, up from 59% in April 2020. Of those respondents who had medical appointments canceled because of the pandemic, 85% were offered a telemedicine alternative, compared with 65% in April.

Acceptance of telemedicine was also high, with 88% of those who said they had been offered a telemedicine visit agreeing to it, and 92% reporting their telemedicine visits as positive experiences.

The report goes on to add, however, that the use of telemedicine has declined since its peak in mid-April 2020.

“NORD has and will continue to advocate for people with rare diseases to have the best possible options and access to medical care,” the report states.

PPE and medications

Even before the COVID-19 pandemic, nearly half of all respondents to the NORD survey regularly used PPE to help them manage infection risks associated with their diseases, and about one in five of these respondents said they required PPE continually.

In addition, many respondents reported widespread lack of precautions by others they came in contact with, such as failure or refusal to wear face masks or to follow common and well-understood social distancing guidelines.

“Most people in my area refuse to wear masks. I wish they would so that I would feel more comfortable in venturing out,” one respondent wrote.

Equally troubling for many was the difficulty in getting access to medications. Some drugs commonly used in cancer care, such as dexamethasone, were reported to be in short supply. Some patients reported delays in receiving oral medications via mail in concert with the widely reported disruptions in the U.S. Postal Service linked to budget cutbacks.

More questions than answers

The NORD report also documents the uncertainties that patients with rare diseases and their caregivers live with, such as unknowns about the effects of COVID-19 on people with rare diseases, whether children at high risk can safely return to school, the efficacy and safety of potential vaccines, and conflicting information on health protocols and resources.

To help people with rare diseases, NORD has created a COVID-19 resource center, available at rarediseases.org/covid-19, which offers links for on-demand videos and webinars, information and tools for advocacy, disease-specific resources for patients, and links to other sources of information that may be helpful for patients and caregivers.

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New agents boost survival – and complexity – in chronic lymphocytic leukemia

Combination therapies now in clinical trials offer even more potential for dramatic improvement.

BY RANDY DOTINGA

Not too long ago, chemoimmunotherapy was the main treatment for chronic lymphocytic leukemia, and it often worked – for a while at least. But the cancer often returned after the first round, and the effectiveness of the treatment weakened. Now, not even a decade into CLL’s targeted-therapy revolution, a long list of new drugs – with more on the way – is transforming extended survival from a possibility into a probability. Combination therapies now in clinical trials offer even more potential for dramatic improvement.

“From 2014 onward we’ve had one or two agents approved per year,” said hematologic oncologist Anthony Mato, MD, MSCE, director of the chronic lymphocytic leukemia program at Memorial Sloan Kettering Cancer Center in New York. As a result of the flood of new therapies, “most of our patients do live long lives and go on to have issues with their other medical problems that are unrelated to CLL.”

The challenge for physicians is to juggle the results of various crucial tests and navigate the targeted-treatment landscape, which is complicated by various side-effect profiles, high cost, drug resistance, and other factors. Choosing a drug – or a combination of drugs – is a complex decision. “While the great news is that lots of these new agents are actively working in historically poor-risk patients, most of the clinical trials that have led to approval have not compared them to each other,” said Dr. Mato.

Still, CLL is “turning into a chronic disease, like diabetes or hypertension, with daily oral therapies,” said Alexey Danilov, MD, PhD, of City of Hope in Duarte, Calif. “We manage it just like we do with elevated blood pressure or acid reflux disease.”

Staging crucial

As in the past, the treatment process starts with disease staging based on guidelines from the International Workshop on CLL. There’s also a predictive tool, the CLL International Prognostic Index (CLL-IPI), but hematologic oncologist Catherine C. Coombs, MD, assistant professor of medicine at the University of North Carolina at Chapel Hill, said it should be used with caution because it underestimates patient survival. “The prognosis overall [now] is quite excellent compared to what the older prognosis models may suggest,” she said, adding that the statistics need to be updated to take novel agents into account.

A 2020 analysis in Clinical Lymphoma, Myeloma & Leukemia also questioned the value of predictive indexes (PIs) like CLL-IPI that aim to offer insight into time to first treatment in early-stage CLL: “[A]lthough all these PIs improve clinical staging and help physicians in routine clinical practice, it will be necessary to harmonize larger cohorts of patients to define the best PI for treatment decision-making in the real world.”

Genetic testing key

Before therapy begins, testing for prognostic markers is crucial, physicians said. According to a 2020 CLL treatment review in the New England Journal of Medicine, written by hematologic oncologist Jan A. Burger, MD, PhD, of the University of Texas MD Anderson Cancer Center, “prognostic markers include cytogenetic abnormalities such as del(13q), del(17p), trisomy 12, and del(11q), as well as the mutation status of immunoglobulin heavy-chain variable (IGHV) genes of the B-cell receptor. Patients with one or more high-risk markers – del(17p), del(11q), or unmutated IGHV – characteristically have a shorter time to initial treatment and shorter remissions after chemotherapy-based treatment than patients with the following markers for low-risk CLL: del(13q), trisomy 12, or mutated IGHV.”

However, “current clinical practice is not keeping pace with recommendations and guidelines for prognostic marker testing and subsequent selection of appropriate therapy,” wrote Dr. Mato and colleagues in a 2020 study in Clinical Lymphoma, Myeloma & Leukemia. (Dr. Mato led the study.) “Even with the approval of novel agents and updated guidelines, low rates...
of prognostic biomarker testing may lead to suboptimal therapy choices for patients with unknown risk status.”

Dr. Mato’s 2020 study, of 840 patients with CLL, found low levels of fluorescence in situ hybridization, TP53 mutation, and IGHV mutation testing (31%, 11%, and 11%, respectively). And about a third of patients identified as high risk, with del(17p) or TP53 mutation, received chemoimmunotherapy. Guidelines do not recommend the treatment in that population.

City of Hope’s Dr. Danilov said the rarity of CLL, compared with other kinds of cancer like lung, colon, and breast, may explain why recommended genetic tests aren’t ordered more often. Whatever the case, “genetics should always be investigated before treatment,” he said. “Testing should be 100% so we know what we’re dealing with.”

Chemotherapy fades in popularity
About a third of patients with CLL are asymptomatic and may never need therapy, according to the review in the New England Journal of Medicine. Among chemotherapy options, a combination of the chemotherapy agents fludarabine (Fludara) and cyclophosphamide (Cytoxan) plus antibody immunotherapy via rituximab (Rituxan) has been “the most effective treatment,” according to a 2020 review in Current Oncology Reports. The therapy is known by the initials of the drugs – FCR.

However, newer targeted-therapy options have greatly reduced the popularity of FCR, and research continues to support alternatives to the treatment. In 2020, the FDA allowed ibrutinib (Imbruvica), a Bruton’s tyrosine kinase (BTK) inhibitor, to be combined with rituximab for a chemotherapy-free frontline treatment of CLL. The FDA based its decision on an ECOG-ACRIN randomized, controlled, open-label, phase 3 E1912 trial of 529 patients. Progression-free survival (PFS) at 3 years was higher for patients who took ibrutinib and rituximab compared to those who took the FCR combination (89% vs. 73% at 3 years, HR = 0.35 for progression or death; 95% CI, 0.22-0.56; P < .001). Overall survival was also higher in the ibrutinib-rituximab group (99% vs. 92%, HR = 0.17 for death; 95% CI, 0.05-0.54; P < .001).

Reflecting the value of genetic testing in providing insight into the most effective treatments, the study found a wide gap in progression-free survival in patients without the IGHV mutation: Those who took ibrutinib-rituximab fared better than the chemoimmunotherapy group (91% vs. 63% at 3 years; HR for progression or death = .26; 95% CI, 0.14-0.50).

There’s still a place for FCR in CLL treatment, Dr. Coombs said, but it’s limited given its toxicity. The National Comprehensive Cancer Network’s 2019 guidelines on CLL for patients note that if “you are younger and healthy enough, fludarabine-based chemoimmunotherapy may be received. Fludarabine is a purine analog, which can cause serious infections.”

Dr. Coombs said she usually doesn’t consider FCR as a treatment option “except for a small subset of patients with mutated IGHV who are relatively young and fit.”

Ibrutinib: ‘Preferred option as first-line therapy’
Targeted therapy is highly recommended for patients at higher risk, and there are many options. “There’s not a clear winner. It’s a matter of having several great options for patients,” said Dr. Mato. He urges physicians to consider their own comfort level in using specific agents along with clinical data and patient characteristics such as comorbidities.

Ibrutinib, the BTK inhibitor, has become a favorite in recent years, gaining wide support as a frontline treatment. The 2020 review in Current Oncology Reports supports ibrutinib (Imbruvica) as “the preferred option as first-line therapy in old and young patients,” although it notes that the necessity for ongoing therapy can spur resistance. The NCCN also lists ibrutinib as the “preferred” first-line treatment regardless for the “young and fairly healthy” and, regardless of presence of del(17p) and TP53 mutation, the “older or sick.”

Dr. Danilov cautioned that BTK inhibitors can cause side effects that are different than those commonly seen from chemotherapy agents. “There are some cardiovascular effects such as elevated blood pressure, and early on, there is a risk of bleeding and rash.”

The 2020 CLL treatment review in the New England Journal of Medicine noted that atrial fibrillation is more likely in patients treated with ibrutinib, but “most patients with atrial fibrillation received medical management, including anticoagulant therapy, and did not need to permanently discontinue ibrutinib.”

Combination therapy on the rise
In addition to its combination with rituximab, ibrutinib has been approved by the FDA in combination with other drugs.
Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is an aggressive and deadly hematologic cancer with skin lesions that may be mistaken for other skin disorders.\(^1\)\(^2\)

Research has uncovered key markers, including CD\(_{123}\), that allow for the proper diagnosis of BPDCN.\(^6\)

Plasmacytoid dendritic cells invade the dermis where they proliferate, resulting in skin lesions that take the form of\(^1\)\(^3\)\(^6\):• Nodular lesions
• Diffuse bruise-like macules

Research has uncovered key markers, including CD\(_{123}\), that allow for the proper diagnosis of BPDCN.\(^6\)

**WHO ARE PATIENTS WITH BPDCN?**

- \(\sim 85\%\) to \(90\%\) present with skin lesions\(^2\)\(^4\)
- \(\sim 75\%\) are men\(^2\)\(^5\)
- Typically between \(60\) to \(70\) years of age, but all ages can be affected\(^2\)\(^5\)

For more information, visit BPDCNinfo.com.

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in CLL, including venetoclax (Venclexta), an inhibitor of B-cell lymphoma 2 protein. For a 2019 phase 2 study in the New England Journal of Medicine, researchers treated 80 patients, 92% with unmutated IGHV, TP53 mutation, or del(11q). “After 12 cycles of combined treatment, 88% of the patients had complete remission or complete remission with incomplete count recovery, and 61% had remission with undetectable minimal residual disease,” the researchers reported. At 1 year, progression-free and overall survival were 98% (95% CI, 94-100) and 99% (95% CI, 96-100), respectively.7

In 2020, a phase 2 study presented at the virtual annual congress of the European Hematology Association linked the ibrutinib-venetoclax combination treatment to deep molecular remissions in both bone marrow and peripheral blood.8

However, “we don’t really know if giving both of those drugs together is better than giving just one of them,” Dr. Coombs said. “There are a number of cooperative group trials comparing ibrutinib-containing regimens to ibrutinib with venetoclax.”

She also noted the CLL14 phase 3 study, whose results were published in the New England Journal of Medicine in 2019. Researchers assigned 432 patients to venetoclax-obinutuzumab (Gazyva) or chlorambucil (Leukeran)-obinutuzumab. At 24 months, the venetoclax-obinutuzumab group had higher PFS at 88% (95% CI, 83.7-92.6) versus 64% (95% CI, 57.4-70.8).9

“The benefit of that regimen in contrast to a BTK inhibitor regimen is that it’s time-limited,” Dr. Coombs said. “A significant proportion of patients will achieve negative MRD [minimal residual disease] status, so that is a very attractive option for patients who want a time-limited regimen.” She cautioned, however, that the study focused on an older population (median age = 72), and researchers are trying to understand venetoclax-obinutuzumab’s effects in a younger population.

As for side effects with venetoclax, Dr. Danilov said it can cause tumor lysis because it kills cells so quickly. As a result, he said, frequent blood tests are necessary.

Acalabrutinib, a second-generation BTK inhibitor

Acalabrutinib (Calquence), a second-generation BTK inhibitor approved by the FDA in 2019, has emerged as an alternative to ibrutinib. “Based on the data, it seems to be comparable to ibrutinib, and there are suggestions that it may have a better side-effect profile,” said Dana-Farber Cancer Institute hematologic oncologist Matthew S. Davids, MD, MMSce, an associate professor of medicine at Harvard Medical School, Boston. “That being said, we have longer-term data with ibrutinib and with high-risk patients.”

The phase 3 ASCEND and ELEVATE-TN trials, of acalabrutinib monotherapy and acalabrutinib/obinutuzumab, respectively, “demonstrated acalabrutinib’s improved efficacy and tolerability” compared with standard treatments, wrote Dr. Mato and a colleague in a review.10

“While it is tempting to speculate that acalabrutinib has similar efficacy to ibrutinib with a favorable side-effect profile, we note that no head-to-head comparative data between acalabrutinib and ibrutinib are available at this time,” the researchers caution. As they note, multiple clinical trials are testing various combinations of acalabrutinib, including combos with venetoclax and obinutuzumab. One active trial, ELEVATE-RR, is pitting acalabrutinib against ibrutinib in high-risk patients who’ve undergone previous treatment. “Since the study is not powered to show superiority of either agent and toxicity is a secondary endpoint, it may not fully address these data gaps regarding differences in efficacy and safety between these two agents,” Dr. Mato and his colleague note.

A three-drug combo tested

There’s a recent twist to the acalabrutinib story: In the ELEVATE-TN trial, “there is a signal for improved progression-free survival” when obinutuzumab is added, Dr. Coombs said. PFS was 90% in the acalabrutinib-obinutuzumab group and 82% in the acalabrutinib group.

“But the significance ends up being pretty modest,” Dr. Coombs said. “Most practitioners aren’t adding obinutuzumab because it does add some toxicity, including neutropenia being the big one.”

As researchers continue to test two-drug combinations, the results of a phase 2 trial of a three-drug combination in high-risk patients have been released. At the 2020 virtual annual congress of the European Hematology Association, researchers noted promising results in the CLL2-GIVE trial of ibrutinib, venetoclax,
and obinutuzumab. The treatment-naïve study tracked 41 patients with del(17p) and/or TP53 mutation. The complete response rate at final restaging was 59%, although the rate of higher-grade infections – 20% – sparked concern. In an interview with Hematology News, Dr. Danilov cautioned that “the question becomes whether using these all at the same time, versus sequential strategies – using one drug and then after that, at relapse, another – is better, and obviously this trial doesn’t address that.”

**Other options: PI3K inhibitors, stem cells, CAR T**

Other treatments for CLL are gaining attention: PI3K inhibitors, including idelalisib (Zydelig), are yet another class of CLL drugs. Because of autoimmune side effects, idelalisib “is not the first-choice kinase inhibitor for CLL therapy, but it is a valuable alternative for patients in whom BTK inhibitors are associated with unacceptable side effects,” reported the 2020 treatment review in the New England Journal of Medicine. Duvelisib (Copiktra) is another available PI3K inhibitor.

Dana-Farber Cancer Institute’s Dr. Davids said the PI3K inhibitors tend to be third-line therapies, often after chemotherapy or BTK inhibitors and then venetoclax. “They’re very active drugs, but they have side effects that need more active management, such as liver inflammation, diarrhea that can become severe, and infections.”

The review also recommends that “allogeneic hematopoietic stem-cell transplantation should be considered in selected younger patients with high-risk disease – those with del(17p), TP53 mutations, or both and a complex karyotype – especially if they have previously received chemoinmunotherapy and subsequently had a relapse.”

Research has found that chimeric antigen receptor (CAR-T) therapy, a cellular immunotherapy strategy, produces “deep remissions – and possibly cures – in some patients with heavily pretreated, high-risk, relapsed, and refractory disease,” write the authors of a 2019 report in American Journal of Hematology.11 “Unfortunately,” they added, “most clinical trials of CAR T cells in CLL report complete responses only in the minority of patients, although recent studies have begun to elucidate the factors most predictive of response.”

The authors of the 2020 CLL treatment review in Current Oncology Reports also offered cautious hope about CAR T: “Small studies of anti-CD19 CAR-T cells in patients who relapsed on BTK inhibitors have shown response rates of over 70% and a survival rate of 100%, although only after 6 months of follow-up. Further larger trials are required, but we can be cautiously optimistic; this may provide a safer alternative to transplantation in patients who fail small molecule therapy.”

Meanwhile, a poster presented at the 2020 Transplantation and Cellular Therapy Meetings tracked 28 patients with CLL in a clinical trial of CART. The study found that overall survival after CAR T was “significantly shorter” in patients who had earlier failed both ibrutinib and venetoclax compared with others. “This finding supports referring high-risk CLL [patients] for CAR T treatment after progression on [ibrutinib] and while still responsive to [venetoclax].” And, they added, allogeneic hematopoietic stem-cell transplantation “seems to provide a higher chance of survival” in patients who progressed after CART.12

Dr. Davids cautioned that CAR T hasn’t been as effective in CLL as in other conditions such as diffuse large B-cell lymphoma. Still, he said, “I think it will have a role in CLL.”

**Where do clinical trials fit in?**

What’s next for research? According to Dr. Davids, clinical trials are offering promising news about umbralisib, a new PI3K inhibitor that may be better tolerated than the existing ones, and LOXO-305 and ARQ 531, a pair of third-generation BTK inhibitors.

Physicians who treat CLL highly recommend clinical trials. The studies generally don’t force patients to take placebos, and most trials pay for treatment, which can be expensive, said Memorial Sloan Kettering’s Dr. Mato.

He added that clinical trials allow researchers to develop better treatments. “There’s certainly tremendous room for improvement since there are still many unsolved problems in CLL such as intolerance and resistance to targeted agents,” he said. “The ultimate goal is to have very long-term control and to develop later lines of therapy for when the current treatment was no longer working. The current generation of clinical trials helps us to answer those questions in addition to the trials that are comparing targeted agents to one another to address the question about what should come first or which is the better agent.”

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Targeted therapies may alter the landscape of MCL treatment

BY JIM KLING

Mantle cell lymphoma is a relatively rare disease, making up 5%-10% of non-Hodgkin lymphoma, and some treatment strategies are still up for debate. Recent advances in therapy, including Bruton’s tyrosine kinase inhibitors that first gained FDA approval in 2014, have improved outcomes, but the disease is still considered incurable.

The comparative rarity and heterogeneous clinical presentation of mantle cell lymphoma (MCL) have posed challenges to clinicians. But new targeted therapies, sometimes combined with chemotherapy or existing targeted therapies, are shaking up both first-line and second-line therapies for MCL. In particular, the July U.S. Food and Drug Administration approval of CAR T-cell therapy for MCL represents a new therapeutic opportunity for patients who have relapsed following Bruton’s tyrosine kinase (BTK) inhibitors.

Classical MCL grows from B cells that express SOX11 and are genetically unstable, leading to acquisition of additional mutations and development of more aggressive disease. Some patients experience stable disease, even without chemotherapy, and this appears to be attributable to greater genetic stability. However, such patients can still acquire mutations that lead to aggressive disease.

Clinicians often defer additional treatment in asymptomatic cases with a low tumor burden, no nodal involvement, and genetic stability. When patients require treatment, they generally receive rituximab plus a cytarabine-based chemotherapy regimen, although there are milder regimens for patients unfit for intense chemotherapy. Rituximab binds CD20, found primarily on mature B cells and more than 90% of B-cell non-Hodgkin lymphomas, and this inhibition promotes cell lysis.

Younger, fitter patients are treated with rituximab with a high-dose cytarabine-based chemotherapy backbone, followed by an autologous stem cell transplant and maintenance with rituximab.

Treatments not optimal

Although these first-line strategies have achieved successes, there is plenty of room for improvement. For one thing, upfront stem cell transplants are expensive and arduous, and not everyone is certain of their benefit. One study showed a progression-free survival benefit but no improvement in overall survival in young transplantation-eligible patients with MCL.

“We are trying to answer the question, ‘do all patients need consolidative stem cell transplants?’ We’re trying to see if an MRD [minimal residual disease]-driven approach could be taken,” said Narendranath Epperla, MD, assistant professor of hematology at the Ohio State University Comprehensive Cancer Center, Columbus.

Such a strategy could involve induction chemotherapy and, in patients who achieve a complete response, MRD testing using immunoglobulin high-throughput sequencing to detect circulating tumor DNA would help guide the next step. The Eastern Cooperative Oncology Group (ECOG 4151) is conducting a trial where patients who achieve MRD negativity would be randomized to either rituximab maintenance therapy or autologous stem cell transplant followed by maintenance rituximab (NCT03267433). “The idea behind the study is to see if we can safely avoid autologous stem cell transplant in those who achieve MRD negativity without compromising efficacy, given the toxicity and resource utilization associated with transplantation. However, we need to await the results of the ECOG 4151 before abandoning the autologous transplantation,” said Dr. Epperla.

Clinical trials ongoing

Additionally, many clinical trials are ongoing examining novel therapies in the frontline setting, in combination with either other novel agents or with chemotherapy. Candidates include BTK inhibitors with a novel mode of action, chemotherapy

Dr. Epperla reports relationships with Pharmacyclics and Verastem.
combined with BTK inhibitors or B-cell lymphoma-2 (BCL-2) inhibitors, anti-CD20 monoclonal antibodies combined with BTK inhibitors or BCL-2 inhibitors, BTK inhibitors combined with immunomodulators, and others. Those trials will no doubt guide future frontline therapy, “but for the time being the paradigm is still rituximab, cytarabine-based chemotherapy until we have readouts on these clinical trials in the frontline setting,” said Dr. Epperla.

Another area of study is combining BTK inhibitors with either chemotherapy or other novel agents in both the relapsed/refractory and frontline settings. Treatment with intensive induction therapy in the frontline setting is also a matter of debate, with some suggesting that it may be unnecessary. “Studies using novel agents in the frontline setting will help answer that in the coming years,” said Dr. Epperla.

After relapse or progression on first-line therapy, BTK inhibitors are generally the treatment of choice. In a pooled analysis of 370 MCL patients, BTK inhibitors provided the most benefit when used in the second-line setting. “Based on that data, it is important to use BTK inhibitors in the first relapse to maximize the outcomes,” said Dr. Epperla.

Choosing an inhibitor

There are three FDA-approved BTK inhibitors, and the choice for Dr. Epperla depends on patient comorbidities. “If they have underlying cardiac issues, I usually choose one of the new BTK inhibitors such as acalabrutinib or zanubrutinib,” he said.

Other therapies on the horizon include novel BTK inhibitors such as LOXO-305 and ARQ 531 being developed by LOXO Oncology and ArQule, respectively. LOXO-305 binds to BTK noncovalently, unlike ibrutinib, acalabrutinib, and zanubrutinib, which all act by covalent binding. This property gives LOXO-305 higher affinity and selectivity for BTK in addition to inhibition of the C481S mutation. ARQ 531 is a reversible multikinase inhibitor of not only BTK but the Src, Syk, and Fyn kinases. Multifaceted upstream kinase inhibition in the B-cell receptor pathway may enhance efficacy over downstream inhibition of BTK alone.

“Mechanistically they seem to be superior [to the existing BTK inhibitors], in that they may be able to overcome the resistance commonly mediated by BTK inhibitors, but I’ll be interested to see how the data pans out in the clinical trials,” said Dr. Epperla.

New options

A couple of recent studies in the relapsed/refractory setting have provided some tantalizing new hope for patients. In particular, CART-cell therapy received FDA approval for the treatment of refractory MCL in July. Kite Pharma developed the regimen, called KTE-X19. CAR-T cell regimens are also FDA approved for large B-cell lymphoma, diffuse large B-cell lymphoma, primary mediastinal B-cell lymphoma, high-grade B-cell lymphoma, and transformed follicular lymphoma.

This spring in the New England Journal of Medicine, researchers published encouraging results of an anti-CD19 CAR T-cell therapy in patients with relapsed/refractory MCL, who had progressed after treatment with BTK inhibitors. This treatment had already shown efficacy in relapsed/refractory aggressive B-cell lymphoma. The technology overcomes a limitation in some patients who have a high proportion of leukemic blasts in the peripheral blood and relatively few T cells available for harvest: It removes CD19-expressing malignant cells in leukemia and MCL patients, thus reducing cells that could activate and inhibit anti-CD19 CART cells during the manufacturing process.

In the open-label, multicenter phase 2 ZUMA-2 trial, 74 patients underwent leukapheresis. All patients had previously been treated with BTK inhibitors and either were refractory (62%), had a progression after an initial response (26%), or were otherwise unable to be treated with BTK inhibitors. Manufacture was successful for 96% of cases, and 92% of patients received treatment. After undergoing conditioning chemotherapy with fludarabine and cyclophosphamide, patients received a single infusion of KTE-X19.

A total of 60 patients had at least 7 months of follow-up, with an objective response rate of 93% (95% CI, 84%-98%), while the complete response rate was 67% (95% CI, 53%-78%). Among the overall group of 74 patients, 85% had an objective

Micrograph of mantle cell lymphoma of the terminal ileum.
response and 59% had a complete response. Subgroup analyses showed no significant differences in response rate, including among patients with high-risk features. The median time to initial response was 1 month (range, 0.8-3.1), with a median time to complete response of 3 months (range, 0.9-9.3).

The study showed that 42 patients had an initial partial response or stable disease. Of these, 57% went on to a complete response at 2.2 months (range, 1.8-8.3 months). At the cutoff date, with a median follow-up of 12.3 months, 17 patients continued to experience a response.

Promising results
The researchers assessed minimal residual disease in 29 patients. At week 4, 24 of 29 (83%) had no detectable residual disease. Of 19 patients with available data at 6 months, 15 patients (79%) were still negative. Overall, 57% of patients who had achieved a response were still in remission at the data cutoff point of around 30 months, including 78% who achieved a complete response. The 12-month estimated progression-free survival (PFS) was 61%, and overall survival was 83%. PFS at six months was similar in patients with and without prognostic features, such as pleomorphic morphologic characteristics, TP53 mutation, or a Ki-67 proliferation index of 50% or higher. Overall survival at the time of analysis was 76%.

A grade 3 or higher adverse event was experienced by 99% of patients; 94% had cytopenia, and 91% experienced cytokine release syndrome (15% grade 3 or higher), though none died of it; 63% of patients had neurologic events (31% grade 3 or higher). Of the 24% of patients who died, 21% succumbed to progressive disease.

The data was impressive, especially considering that patients were high risk, with previous exposure to BTK inhibitors. “It further adds to the credence that CAR T seems to be really effective in this patient population. These are early days. I want to see how the data pans out in the long term, but for now I’m definitely impressed by the CAR T data,” said Dr. Epperla.

If BTK inhibitors fail to slow the disease, Dr. Epperla thinks CAR T-cell therapy should be the next choice. “If people progress on BTK inhibitors, their outcome is not great. That’s why they go on to either clinical trials or CAR T, because none of the studies has shown superior outcomes once they progress on BTK inhibitors,” said Dr. Epperla.

Other options on the horizon
Still, CAR T-cell therapy isn’t the only development. Targeted agents have also provided new hope in MCL treatment. One such class of agents includes mammalian target of rapamycin (mTOR) inhibitors, which have been studied in a wide range of solid and hematologic tumors. mTOR is a master switch that controls protein translation, part of the PI3K/AKT/mTOR pathway. When activated, mTOR boosts messenger RNA translation of growth proteins such as cyclin D1, c-MYC, and hypoxia-inducible factor 1 alpha. mTOR activation increases cellular proliferation and inhibits autophagy, which is the recycling or degradation of cellular material. It also regulates production of oncogenes that have been implicated in lymphomagenesis.

Application of mTOR inhibitors to lymphoma was driven by overexpression of cyclin D1, and the mTOR inhibitor temsirolimus has shown efficacy in relapsing/refractory MCL. But single-agent treatment rarely achieves complete or long-term remissions. Addition of rituximab to temsirolimus has been studied in relapsed/refractory MCL, with 59% overall and 19% complete remission rates. Temsirolimus has also shown promise combined with cytotoxic therapy.

Looking to triplet therapy
To examine the efficacy of triplet therapy, including temsirolimus, rituximab, and bendamustine, researchers at German institutions conducted a phase 1/2 clinical trial with 39 patients, including 29 with MCL and 10 with follicular lymphoma (FL). A total of 15 patients were included in the phase 1 portion (11 with MCL). Patients had undergone a median of two prior regimens, and all had previously received rituximab.

Nine patients had previously received bendamustine. Thirty-five percent had achieved at least a partial response to their most recent therapy, while 60% were refractory; 41% had progressive disease.

In the phase 1 study, patients received 25, 50, or 75 mg temsirolimus. The phase 2 study included 27 patients, all of whom received the 75 mg dose, and 65% of planned cycles were completed. Of 37 evaluable patients, 89% of MCL and 90% of FL patients had an objective response.
Overall, 38% achieved complete remission, including 44% of MCL and 20% of FL patients. Eleven percent of patients overall had stable disease.

“If the rate of [stable disease] is added to [complete response and partial response], it would result in a clinical benefit rate of 100%,” the researchers wrote. They later added: “Keeping in mind that [the regimen] was intended to be a short-duration treatment (only four cycles were given), these response rates are encouraging. Considering that 60% of the study population had not responded to their individual last treatment line, this underlines that the combination is able to overcome drug resistance in a substantial proportion of patients.”

A total of 26 of 28 patients experienced a response after the second cycle (two complete). After a median follow-up of 2.7 years, the median progression-free survival overall was 1.5 years for MCL patients (95% CI, 0.84-3.55) and 1.82 years for FL patients (95% CI, 0.64 to unknown). Neither group reached median overall survival, but 3-year survival was 56% for MCL and 58% for FL.

Among 39 patients who received the study treatment, adverse events included leukopenia (72%), thrombocytopenia (64%), neutropenia (51%), lymphopenia (41%), and anemia (28%). Grade 3/4 hematologic adverse events overall included leukopenia (56%), neutropenia (46%), lymphopenia (41%), and thrombocytopenia (36%). Three patients needed one or more platelet transfusions, and 12 used granulocyte colony-stimulating factor.

Nonhematologic treatment emergent adverse events included fatigue (64%), nausea (56%), mucositis (49%), diarrhea and rash (38%), pyrexia (36%), constipation (33%), and cough (31%). Grade 3/4 nonhematologic adverse events included hyperglycemia (10%) and angioedema (5%). Twenty-three percent had grade 3/4 infectious complications.

The results offer another option for MCL management. “I like the limited duration therapy because we’re pushing for time-limited, MRD-based approaches in the lymphoma community where patients are not on these novel agents forever, not only to limit toxicities but also to limit the financial burden,” said Dr. Epperla.

He also noted that the combination seemed well tolerated, and the study had a high response rate. One drawback to the trial is that it did not include patients treated with BTK inhibitors, likely because the trial was initiated before BTK inhibitors were approved. “[For BTK relapers,] would the response still be that high? That’s an unanswered question,” said Dr. Epperla.

Looking to bispecifics
Also in the relapsed/refractory setting, Dr. Epperla is keeping an eye on bispecific antibodies. These agents bind to both CD3 and CD20. They have shown promising results in relapsed/refractory B-cell non-Hodgkin lymphoma. Researchers at the American Society of Hematology showed an overall response rate of 37% in relapsed/refractory aggressive B-cell non-Hodgkin lymphoma with activity noted in those who relapsed following CART-cell therapy.

MCL-specific response rates were not reported, but “I’m very excited to see how bispecifics get incorporated into the treatment paradigm when you have such a plethora of agents to choose from, including novel agents, monoclonal antibodies, and antibody-drug conjugates. Although it is an exciting time to be a lymphoma physician, the job is not done until we find a cure for these patients,” said Dr. Epperla.

REFERENCES
Scores of companies and academic research labs across the globe are working on chimeric antigen receptor T-cell therapies. Billions of dollars have been invested, and the CAR T-cell therapy market is projected to be worth more than $7 billion by 2028.

More than 600 CAR T-cell therapy trials are active worldwide, and the Food and Drug Administration is processing more than 900 investigational new drug applications of cell and gene therapies, including for hematologic malignancies and solid tumors, according to a presentation at the American Society of Clinical Oncology annual meeting.

The massive influx of brain power and capital is driven by the success of the three CAR T products already on the U.S. market: axicabtagene ciloleucel (Yescarta) for relapsed or refractory large B-cell lymphoma; tisagenlecleucel (Kymriah) for relapsed or refractory large B-cell lymphoma and B-cell precursor acute lymphoblastic leukemia in patients up to 25 years old; and brexucabtagene autoleucel (Tecartus) for relapsed or refractory mantle cell lymphoma. Trials report durable, years-long remissions in up to 40% of patients who had exhausted other medical options and generally weren’t expected to live past 12 months.

The common denominator for the three U.S. products is that T cells are drawn from the patient and sent to a company-accredited lab. Once there, a retroviral or lentiviral vector is used to introduce DNA into the cells so that they express a chimeric receptor against the CD19 antigen expressed on the targeted cancer cells. The T cells are then sent back to the clinic and infused into the patient, where they go to work against their cancer.

What’s gotten industry and academia so excited is the proof of concept that immune cells can be reprogrammed to attack, conceivably, anything that goes wrong in the body. With CRISPR gene editing and other recent advances, the technology is already in place to engineer immune cells to do whatever is needed. Approval is expected soon for a multiple myeloma treatment, and work is ongoing for other blood cancers and solid tumors, as well as life-threatening infections, rheumatoid arthritis, multiple sclerosis, diabetes, organ transplant rejection, and other problems.

Dr. Stephen Gottschalk has patent applications in the fields of T-cell and/or gene therapy for cancer and a research collaboration with TESSA Therapeutics. He is a member of Immatics’ Data and Safety Monitoring Board, and an advisor to Tidal. Dr. Sadelain has collaborative research agreements to develop new CAR therapies with Takada, Fate, and Atara.
A chess game against solid tumors

Solid tumors are a prime focus of research. Investigators are swinging for a home run, but it hasn’t happened yet.

There have been scores of reports at ASCO and other meetings of CAR Ts for brain, ovarian, lung, gastrointestinal, and other cancers, but the studies have been generally small with only modest benefits in a few patients.

The reason is because there are “major roadblocks” to overcome for solid tumors, Dr. Gottschalk said.

The biggest problem is finding the right antigen to target. The idea is to find one that’s expressed only on solid tumors to avoid “on-target, off-tumor” toxicity. Nothing to date has emerged to rival the specificity of CD19 for lymphomas. The only healthy cells that express it are B cells; they, too, are wiped out during therapy, but that’s manageable with immunoglobin replacement.

Researchers like Dr. Gottschalk don’t know if specific antigens will ever be found for solid tumors, so many are trying other approaches. One is to go after antigens expressed preferentially on solid tumors, with low frequency in healthy tissues. Another is to look for constellations of antigens that may individually be expressed on healthy tissues but appear together only on tumor cells. “That is where I think probably the solution is; we design a CAR T which only gets fully activated if it sees the right pattern, he said.

Another problem is that solid tumors have a hostile microenvironment that shuts off immune cell activity; a lot of research now is on engineering T cells that can best these tumor adaptations. With CRISPR, for instance, “you can insert a second gene to express a cytokine that makes a cold tumor hot” or otherwise overcome the immunosuppressive microenvironment. Also, “you can try to edit genes in T cells so that they are hyperactive,” or even invisible to the tumor’s defenses, Dr. Gottschalk said.

Another research tactic is to kill cells that support the tumor, including tumor-associated fibroblasts and tumor vasculature. CAR Ts also need help finding solid tumors. It’s easy with blood cancer because they migrate to the bone marrow; for solid tumors, researchers are engineering in homing receptors to help CAR Ts zero in.

CARs are also being introduced into other immune cell types, particularly natural killer (NK) cells. University of Texas MD Anderson Cancer Center, Houston, recently reported complete remissions in 4 lymphoma and 3 chronic lymphocytic leukemia patients, out of a total of 11 subjects, with NK anti-CD19 CAR cells. NK cells are quicker and better killers than T cells, but they don’t persist long. “You might in the end have to infuse a combination of cells,” where NK cells do a lot of the initial debulking as the CAR T cells ramp up to take care of the rest, Dr. Gottschalk said.

There are no guarantees that any of it will work, but with the current pace of research, “I think solid tumors are within reach. I am optimistic that in the next 5 years, we are going to see some really provocative trials,” said Sloan Kettering’s Dr. Sadelain.

Not a breakthrough if not used

Despite the advances, there were various reports at the ASCO meeting that many people eligible for current CART treatments aren’t getting them.

Part of the problem is clinical. Among other hurdles, the logistics of collecting the cells and manufacturing them into CAR Ts can take weeks, and the process is expensive. Successfully doing so from patients heavily pretreated with lymphodepleting therapies is challenging, as is ensuring that the final product isn’t contaminated with their own malignant cells.

The problems have led to efforts to manufacture off-the-shelf CAR T cells from healthy donors. With CRISPR and other techniques, it’s now possible to edit out the immunogenic components of donor cells and eliminate the risk of graft-versus-host reactions, the main concern. “We have this in an ongoing clinical trial right now with no data just yet,” but the approach “is showing exciting activity early on,” said Jeremy Abramson, MD, director of the Jon and JoAnn Hagler Center for Lymphoma at Massachusetts General Hospital, Boston, at the ASCO meeting.

Allogenic cells would also eliminate the need to manufacture fresh cells from each patient, reducing both the time to treatment and costs, another hurdle to widespread access.

Right now, one-time treatment with CAR T cells is in the neighborhood of $400,000 for the cells themselves; with apheresis, clinical care to manage infusion complications, and other issues, the price tag approaches $500,000 per infusion. Currently, Medicare reimburses hospital cases at the same rate as bone marrow transplants, which are considerably below that mark, plus a temporary new technology add-on payment set to expire at the end of the year.

The Centers for Medicare & Medicaid Services, however, recently proposed a new hospital payment category for...
CAR T therapy that could close most of the gap, a new Medicare Severity Diagnostic Related Group for CAR T therapy that “will provide a predictable payment rate for hospitals administering the therapy. This is another example of CMS’s commitment to ensuring that beneficiaries have access to the latest medical innovation,” the agency said in its announcement.

“Inadequate reimbursement can significantly limit the ability of rare disease patients to access these innovative treatments, as providers are unlikely to offer care and treatments for which they will not be sufficiently compensated. … We encourage CMS to finalize this proposal,” the National Organization for Rare Disorders said in a response letter.

**Improving on already remarkable results**

Meanwhile, work is ongoing to improve outcomes with products already on the market. Although “anti-CD19 CAR T cells are truly transformational therapy in chemotherapy” for refractory large B-cell lymphoma and B-cell acute lymphoblastic leukemia (ALL), and “hopefully soon, multiple myeloma,” only up to 40% of patients have durable remission. “Not everybody is cured. We still have work to do,” Dr. Abramson said.

“I think we get there by targeting mechanisms of resistance to CAR T-cell therapy; that includes” antigen escape, meaning loss of the CD19 antigen after the cells are infused; poor proliferation or persistence of CAR T cells in heavily pretreated patients; and other problems.

Two major avenues of research address the issues: combining T-cell therapy with existing treatments and further genetic engineering to improve CAR T-cell activation, expansion, persistence, and antitumor efficacy.

One problem is that PD-1 and other immune checkpoints are induced on CAR T cells after infusion.

Dr. Abramson recalled a 42-year-old man who, after failing conventional therapy for mediastinal large B-cell lymphoma, responded to tisagenlecleucel, but his remission lasted only 3 months. A second round of CAR T cells had no effect, suggesting immune escape.

“We treated the patient with pembrolizumab,” a PD-1 immune checkpoint inhibitor. He went into a complete remission in 2 months and remains in complete remission more than 2 years later.

What happened is that the pembrolizumab “triggered a dramatic, robust re-expansion of the CAR T cells, coinciding with the patient’s reentering complete remission, highlighting that CAR T-cell therapies are not a one-time treatment, but rather a platform, a cellular therapy, a living drug that can be manipulated with ongoing interventions … to enhance their antitumor efficacy,” Dr. Abramson said.

It doesn’t always work. “In fact, in early studies right now, the majority [of patients] have not had [such] robust responses,” but the story illustrates that improving CAR T outcomes is possible “and warrants exploration going forward,” he said.

**A reprise from transplant?**

There’s also research into how CD19 CAR T therapy fits in with current treatments, including replacing bone marrow transplants in lymphoma.

“Right now, we are refining the patient population [where] that would be possible,” Dr. Gottschalk said.

A study was announced at the ASCO meeting to test whether tisagenlecleucel can enable children and young adults with B-cell precursor ALL and persistent residual disease after two cycles of frontline, high-risk chemotherapy to avoid transplant altogether.

Although “CAR T cells are not without toxicities … with the most prominent acute toxicities being [cytokine release syndrome] and neurotoxicity, prior trials have shown that the rates of severe toxicities are much lower in patients with” residual disease, said Shannon Maude, MD, PhD, from the Children’s Hospital of Philadelphia, at ASCO.

A collaboration of the Children’s Oncology Group and several European centers, the study has as a primary objective to determine 5-year disease-free survival.

Patients undergo leukapheresis at the time of screening, after consolidation, or in the next phase of chemotherapy, or earlier at the end of induction if they have high-level measurable residual disease. They continue with standard therapy and receive high-dose methotrexate and interim maintenance while cells are being manufactured. After infusion, patients receive no further planned therapy and are followed for residual disease and persistence of CAR T cells, as well as for toxicity.

“The trial will define CAR T’s role in frontline therapy, as well as begin to answer the question of whether we can eliminate transplant for some children and young adults with [B-cell] ALL,” Dr. Maude said.

“Time will show what works. The possibilities are very extensive,” Dr. Sadelain said.

**REFERENCES**

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