Sequencing Therapies in Indolent Lymphomas

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Many targeted agents have emerged for treating chronic lymphocytic leukemia (CLL), which has made treatment selection more complex, according to Philip A. Thompson, MB, BS, assistant professor in the department of leukemia at The University of Texas MD Anderson Cancer Center. Dr. Thompson described the growing therapeutic landscape of CLL as well as follicular lymphoma at JADPRO Live 2018. Dr. Thompson was joined by Lisa Nodzon, PhD, ARNP, AOCNP®, of the department of malignant hematology at Moffitt Cancer Center, who discussed the management of toxicities related to newer agents.

FRONT-LINE THERAPIES IN CLL

"In CLL, we've seen an amazing number of new, approved therapies in the past few years that target key biological processes," Dr. Thompson noted. He listed second-generation anti-CD20 monoclonal antibodies (ofatumumab [Arzerra] and obinutuzumab [Gazyva]), a Bruton tyrosine kinase (BTK) inhibitor (ibrutinib [Imbruvica]), phosphoinositide 3-kinase (PI3K) inhibitors (idelalisib [Zydelig] and duvelisib [Copiktra]), and a B-cell lymphoma 2 (BCL2) inhibitor (venetoclax [Venclexta]). "It feels like we're in the myeloma world, as we start stacking treatments on top of each other," Dr. Thompson commented.

The current first-line treatment of CLL centers upon chemoimmunotherapy (fludarabine/cyclophosphamide/rituximab [FCR], bendamustine/rituximab (BR), chlorambucil/obinutuzumab or chlorambucil/ofatumumab), and monotherapy with ibrutinib. The aims are (1) to achieve undetectable minimal residual disease (MRD), as patients with MRD-negative status have longer progression-free survival (PFS); (2) to treat for a limited duration; and (3) for treatment to be well-tolerated. Unfortunately, none of the current front-line regimens achieves all three aims. "Ibrutinib rarely achieves complete remissions and undetectable MRD. FCR, in contrast, can achieve a high rate of MRD negativity but is less well tolerated," Dr. Thompson said.

In patients older than 65, BR is better tolerated than FCR and offers better PFS benefits only in patients with *IgHV* mutations (Eichhorst et al., 2016; Thompson et al., 2016,

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2018). "With FCR you have the opportunity to potentially cure a patient with mutated *IgHV*, particularly if they achieve MRD negativity," he said. He therefore incorporates *IgHV* mutation status into decision-making.

Outcomes are "dismal" after FCR for patients with del(17p) and for those with *TP53* mutations. For these subsets, chemoimmunotherapy is not sufficient, and ibrutinib is now the standard of care. In a 2016 study by O'Brien and colleagues, median PFS at 2.5 years had not been reached (O'Brien et al., 2016), "which is a dramatic advance over a PFS of about 1 year with FCR," Dr. Thompson commented.

Ibrutinib was approved by the FDA for all patients with CLL on the basis of the RESONATE-2 trial that compared it to chlorambucil/obinutuzumab in patients 65 or older (Barr et al., 2016). The 2-year PFS rate was 89%, and ibrutinib was effective even in patients with unmutated *IgHV* or del(11q).

More relevant to clinical practice today, ibrutinib was compared to BR as front-line treatment in the recently reported phase III Alliance A041202 trial (Woyach et al., 2018). After a follow-up of 32 months, median PFS was 41 months with BR and was not reached with single-agent ibrutinib alone, a 60% reduction in risk.

First-Line Treatment Algorithm for CLL

The first-line treatment selection at The University of Texas MD Anderson Cancer Center begins with a mutation assessment, according to Dr. Thompson. Where available, clinical trials are preferred for all patients. However, outside of clinical trials, patients with del(17p) and/or *TP53* mutation receive ibrutinib, while those without these features receive treatment based on fitness, IgHV mutation status, and del(11q) status (Figure 1). A patient who is *IgHV*-mutated without del(11q) usually receives chemoimmunotherapy, while FCR is preferred for those 65 and younger because of the potential to achieve very prolonged PFS and possible "cure." Patients with unmutated IgHV or del(11q) are offered ibrutinib. Chlorambucil plus obinutuzumab or ofatumumab are also available as first-line treatment, but ibrutinib is generally preferred, given that the PFS rate appears superior.

Potentially Practice-Changing Trials

Ongoing studies in "fit" patients are comparing ibrutinib plus rituximab and venetoclax-based regimens to FCR or BR. Ongoing studies in "unfit" patients are examining acalabrutinib (Calquence; a next-generation BTK inhibitor), ibrutinib, venetoclax, and umbralisib (a next-generation PI3K inhibitor) plus ublituximab (an anti-CD20 antibody); these are all being compared to chlorambucil plus obinutuzumab. "We are going to have a huge array of options for patients, which may make treatment choices in some ways more difficult," Dr. Thompson commented.

TREATMENT OF RELAPSED/REFRACTORY CLL

For relapsed/refractory CLL, four agents in three classes are approved, including a BTK inhibitor (ibrutinib), PI3K inhibitors (idelalisib, duvelisib), and BCL2 inhibitor (venetoclax). There are no head-to-head data to guide their sequencing, only that for patients previously treated with idelalisib or ibrutinib—a growing subset—venetoclax is effective, producing a median PFS of 2 years (Jones et al., 2018).

While venetoclax is approved for all CLL patients, it is particularly effective in patients with del(17p) and can yield a high rate of MRD negativity. In the registration trial, venetoclax proved "dramatically superior" to BR in patients at first relapse, with a 62% rate of undetectable MRD (Seymour et al., 2018). It can also be combined with rituximab without much increase in toxicity over the single agent.

Dr. Thompson's approach is to use ibrutinib or venetoclax, with or without rituximab, for patients naive to both BTK and BCL2 inhibitors. In a nonrandomized study evaluating the optimal sequencing of kinase inhibitors, ibrutinib given first yielded superior PFS over idelalisib, possibly because of better tolerability (Mato et al., 2017), he noted.

Patients intolerant of or refractory to BTK inhibitors can receive venetoclax, idelalisib plus rituximab, or duvelisib. Venetoclax-refractory patients can be tried on ibrutinib while patients refractory to both a BTK inhibitor and venetoclax should be enrolled on a clinical trial or considered for allogeneic stem cell transplant, ideally after a response to salvage therapy.

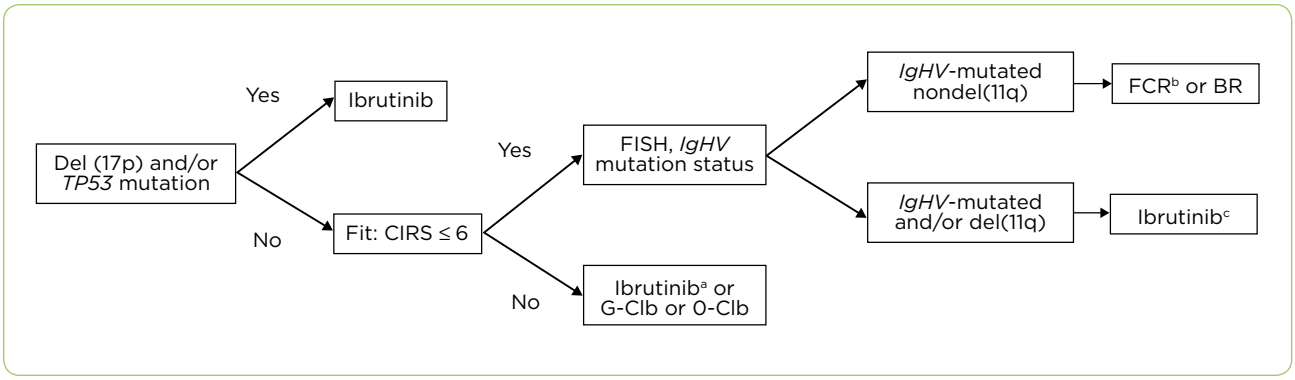

Figure 1. A suggested first-line treatment algorithm for chronic lymphocytic leukemia. CIRS = cumulative illness rating scale; G-Clb = obinutuzumab plus chlorambucil; O-Clb = ofatumumab plus chlorambucil. FCR = fludarabine/cyclophosphamide/rituximab; BR = bendamustine/rituximab. Adapted from Jain et al. (2018).
[a]Ibrutinib preferred unless contraindicated.
[b]FCR preferred in patients ≤ 65 years of age. BR or FCR preferred for patients > 65.
[c]Note, no results of head-to-head comparison with chemoimmunotherapy in first-line setting.

MANAGEMENT OF TOXICITIES FROM TARGETED TREATMENTS IN CLL

Dr. Nodzon then described the toxicities that are seen with targeted agents in CLL and the keys to recognizing and managing them.

Ofatumumab has a number of indications, most recently as maintenance after two lines of therapy. Obinutuzumab is approved for treatment-naive CLL in combination with chlorambucil. Both these anti-CD20 monoclonal antibodies carry black box warnings for hepatitis B virus reactivation and progressive multifocal leukoencephalopathy.

"Prior to therapy, all patients should undergo hepatitis studies and during therapy should be retested if there is a suspicion of reactivation of infection," she said. "Because we are suppressing the immune system, we also watch for progressive multifocal leukoencephalopathy. It's rare, but when patients present with neurological symptoms, keep that in your differential."

Tumor lysis syndrome is another toxicity to watch for. "CLL patients can have bulky lymphadenopathy and very high white blood cell counts, so with rapid cell lysis the patient can develop electrolyte disturbances that can have clinical consequences," she noted.

Infusion-related reactions are common, more so with obinutuzumab than ofatumumab and more in patients with high tumor burden. Since hypotension can occur, antihypertensives should be held on infusion days. Patients with preexisting pulmonary or cardiac conditions need close monitoring because hypoxia and bronchospasm are sometimes seen. Premedication should be tailored to the patient. "For example, we may give a higher steroid dose to a patient with a high disease burden or one with a prior reaction," she said. Antiviral prophylaxis against herpes zoster is recommended, and sometimes bacterial or fungal prophylaxis, growth factors, and antimicrobials.

Ibrutinib has broad approval across front-line and relapsed settings. Due to the mechanistic effects of the drug ("redistribution of lymphocytes"), symptomatic lymphadenopathy can regress within a few days; patients should be forewarned that proliferative lymphocytosis is not a sign of disease progression. Hyperuricemia can be seen and lymphocytes can rise before plateauing and falling. Gout can flare, so clinicians should pay attention to uric acid levels.

In an integrated analysis of the RESONATE and RESONATE-2 trials, after a median exposure to ibrutinib of 29 months, 29% of patients discontinued the drug due to adverse effects, and 12% required dose reductions (Coutre et al., 2016). Most toxicities with ibrutinib, however, are low-grade and easily handled when recognized and treated early, she said.

Dr. Nodzon spent some time discussing ibrutinib-associated bleeding, which can be problematic. Nonsteroidal anti-inflammatory drugs are not recommended and, if required, such as

for arthralgia, they should be used in low doses. A special challenge is the patient with symptomatic atrial fibrillation who may require anticoagulation. The need for anticoagulants in these patients should be formally assessed, ideally with the help of a cardiologist. Hypertension should be carefully managed as well, since the risk of development may increase as a late effect in approximately 25% of patients, which can enhance bleeding risk.

Ibrutinib-associated bleeding is partially reversed after 2.5 days of withholding the drug and is reversible within 1 week of stopping. The drug should be held for 3 days perioperatively in patients having minor surgery, for 7 days for major surgery, and before colonoscopy. In case of a serious bleed, transfusion of platelets is the only means of reversal.

The two PI3K inhibitors, idelalisib and duvelisib, approved in the relapsed setting, pose risks for immune-mediated toxicities. Idelalisib carries a black box warning for hepatic toxicity, diarrhea, colitis, pneumonitis, infections, and intestinal perforation. Duvelisib has essentially the same black box warnings as idelalisib, and recommendations are similar.

In the Study 116 of idelalisib, grade ≥ 3 adverse events included diarrhea/colitis (5%), pneumonia (8%), pneumonitis (4%), transaminitis (8%), and neutropenia (37%; Furman et al., 2014). For diarrhea, the key to management is to first exclude an infectious cause (due to immune suppression). The time of onset provides clues: Within 2 months of treatment initiation, diarrhea is usually mild and management is supportive; for later onset, around 8 months, diarrhea is typically grade ≥ 3, may be associated with electrolyte disturbances, and may require hospitalization. Colitis should be considered for patients experiencing this late-onset diarrhea. Throughout treatment, patients should be monitored for reactivation of cytomegalovirus, and this may require colonoscopy-directed biopsy. For colitis, the recommendation is to hold idelalisib and treat with steroids; budesonide may hasten recovery. "Patients do improve over time, but it requires aggressive supportive care," she commented.

Pneumonitis is rare (< 5%) but can escalate rapidly. "All our patients on PI3K inhibitors get pulse oximetry in the clinic, and if we are concerned about pneumonitis they get a chest CT... Some will even require bronchoscopy with bronchoalveolar lavage," she said. She holds idelalisib if she suspects pneumonitis, and if pneumonitis is confirmed, then permanently discontinues the PI3K inhibitor and treats with steroids. Although rare (3% incidence), *Pneumocystis jirovecii* pneumonia can occur, therefore, prophylaxis is recommended. Hepatotoxicity typically occurs in the first 3 months of treatment. Avoidance of hepatotoxic agents, such as acetaminophen and alcohol, is advised. After dose interruption, most patients can resume treatment. Patients should be monitored for viral reactivation.

Venetoclax is approved as monotherapy for relapsed/refractory CLL with del(17p) and with rituximab in any relapsed/refractory CLL patient. "Venetoclax has a very favorable risk/benefit profile, but the key to giving it is patient profiling before you start the 5-week ramp-up course," Dr. Nodzon said.

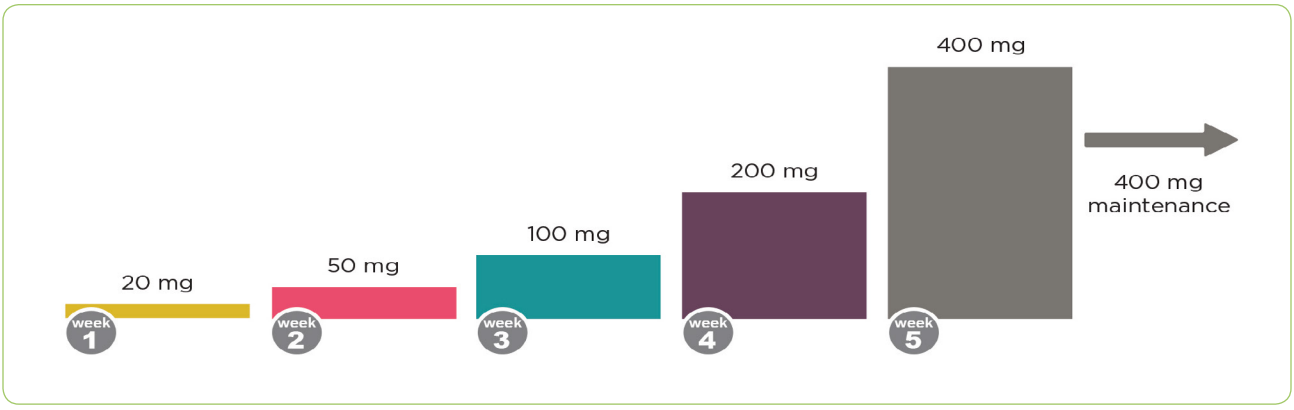

Figure 2. 5-week ramp-up venetoclax schedule. Adapted from Abbvie Inc., & Genentech, Inc. (2018).

During the 5-week ramp-up period (Figure 2), concomitant use of strong CYP3A inhibitors is contraindicated. Adverse events of special interest include autoimmune hemolytic anemia (7%), myelosuppression (64% grade ≥ 3), gastrointestinal disturbance (40% any grade), pneumonia (9% grade ≥ 3), and laboratory tumor lysis syndrome (3%–6% grade ≥ 3). To protect against nausea, venetoclax should be taken with a low-fat meal, as fat increases absorption. Approaches for mitigating tumor lysis syndrome are shown in Table 1.

Based on lymph node size (as shown on computed tomography [CT]) and lymphocyte count, clinicians can risk-stratify patients. "You can treat low- and medium-risk as outpatients and admit high-risk patients," she indicated.

FRONT-LINE MANAGEMENT IN FOLLICULAR LYMPHOMA

Follicular lymphoma is also an indolent lymphoma, but its treatment is very different from CLL, largely because fewer novel agents are available, Dr. Thompson continued. In the first-line setting, chemoimmunotherapy remains the foundation of treatment. A small subset of patients presents with localized disease (stages I–II) that is potentially curable with radiotherapy, although many patients are simply monitored aggressively. Advanced stage at presentation is more common. Symptomatic patients receive chemoimmunotherapy, usually with (1) rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP); (2) rituximab plus cyclophosphamide, vincristine, and prednisone (R-CVP); or (3) rituximab plus bendamustine (BR), with or without rituximab maintenance. In the absence of symptoms, patients can be observed (since early treatment has demonstrated no survival benefit) until they demonstrate Groupe d'Etude des Lymphomes Folliculaires (GELF) criteria: bulky lymphadenopathy, systemic symptoms, compression syndrome, splenic enlargement, pleural or peritoneal effusion, leukemic phase (circulating malignant cells), and cytopenia.

Table 1. Measures to Mitigate Tumor Lysis Risk

Disease burden + antihyperuricemic agent + hydration
Low risk: nodal mass < 5 cm AND ALC ≤ 25,000
• Outpatient dosing at all levels • Postdose labs: 6–8 and 24 hours for first dose of 20 mg and 50 mg
Medium risk: nodal mass 5 to < 10 cm OR ALC ≥ 25,000
• Outpatient: Consider hospitalization if CrCl < 80 mL/min • Postdose labs: 6–8 and 24 hours for first dose of 20 mg and 50 mg
High risk: nodal mass ≥ 10 cm OR ALC ≥ 25,000 AND any node ≥ 5 cm
• Hospitalized for first dose of 20 mg and 50 mg • Postdose labs: 4, 8, 12, and 24 hours for first dose of 20 mg and 50 mg then outpatient for ramp-up doses with postdose labs at 6–8 hours and 24 hours

Note. ALC = absolute lymphocyte count; CrCl = creatinine clearance. Adapted from Abbvie Inc., & Genentech, Inc. (2018).

The choice of chemoimmunotherapy at this time is either BR or R-CHOP. In the STiL study, BR offered superior PFS and better tolerability (Rummel et al., 2016). "We don't use BR for every patient, however, because of the dramatic improvement in outcomes for patients who receive rituximab maintenance after R-CHOP. We don't know if that same benefit is achieved after BR," Dr. Thompson explained. Further complicating the matter, among several treatment arms in the GALLIUM study, most fatal events occurred in older patients receiving bendamustine-based regimens (Marcus et al., 2017).

"Either of those treatments remains a reasonable choice," he concluded, "but, generally, for elderly patients and persons with comorbidities, you would look at a less intensive regimen, such as R-CVP or rituximab monotherapy."

In GALLIUM, obinutuzumab/chemotherapy was superior to rituximab/chemotherapy, reducing the risk of progression by 32% (p = .0016) and reducing the risk of disease progression at 24 months by 42% (Hiddemann et al., 2018). However, obinutuzumab was associated with more infusion-related reactions, febrile neutropenia, and grade 3 infections, and no overall survival benefit was shown. "When choosing a monoclonal antibody, obinutuzumab is a more potent drug, but rituximab is essentially less toxic and lower in cost, and patients who become rituximab-refractory may be able to be salvaged with obinutuzumab. Either remains a reasonable choice," Dr. Thompson maintained.

Rituximab Maintenance

The PRIMA study validated the concept of rituximab maintenance after rituximab/chemothera-

py in follicular lymphoma, showing a reduction in progression and in transformation to diffuse large B-cell lymphoma (Salles et al., 2013). These benefits persisted in the 10-year follow-up, but no overall survival benefit emerged (Federico et al., 2018). In considering maintenance rituximab, clinicians should take into account the induction regimen (the benefit of maintenance after BR is unclear), the patient's tolerance for induction, and the importance of reducing the risk of transformation. They should also remember that maintenance rituximab has not been shown to improve survival.

TREATMENT OF RELAPSED/REFRACTORY FOLLICULAR LYMPHOMA

For the 20% of patients who relapsed within 2 years of primary therapy, 5-year survival is < 50% (Casulo et al., 2015). Two key questions for the management of relapsed/refractory disease are (1) does the patient need treatment or can the patient be managed with active surveillance, and (2) if treatment is desired, how rapid was the prior progression? For progression beyond 24 months, patients can receive chemoimmunotherapy again, and if the patient fails to respond, a clinical trial or novel agent can be considered. If patients progressed within 24 months or on primary therapy, an autologous transplant should be considered, he advised.

Obinutuzumab plus bendamustine is an option for patients who progress on rituximab-based therapy, based on results of the GADOLIN trial of rituximab-refractory (and other poor-risk) patients (Sehn et al., 2016). PFS was significantly prolonged with obinutuzumab/bendamustine vs. bendamustine alone.

The PI3K inhibitors are also approved in relapsed follicular lymphoma, but BTK inhibitors and BCL2 inhibitors have not shown benefit. In the 101-09 study, idelalisib monotherapy produced a 56% response rate and a median PFS benefit of 11 months in patients refractory to two lines of therapy (Gopal et al., 2014). Similar outcomes were achieved with copanlisib (Aliqopa; Dreyling et al., 2017) and duvelisib (Flinn et al., 2016), although altogether, these drugs produce relatively short remissions after second relapse, as compared to their benefit in CLL. "There remains work to be done here," Dr. Thompson commented.

Dr. Nodzon added that copanlisib, as a dual inhibitor of alpha and beta isoforms of PI3K, has some unique toxicities as compared to idelalisib and duvelisib. These are primarily hyperglycemia (50% all grades; 41% grade ≥ 3) and hypertension (30% all grades; 24% grade ≥ 3). While these tend to be transient, she suggested, "Perhaps copanlisib is not the agent of choice for a patient with uncontrolled hypertension or diabetes."

Disclosure

Dr. Thompson has served on advisory boards or received honoraria from AbbVie, Pharmacyclics, Amgen, Genentech, and Gilead, and research funding from AbbVie, Pharmacyclics, Amgen, and Adaptive Biotechnologies. Ms. Nodzon has received consulting fees from and served on speakers bureaus for AbbVie, Genentech, and Gilead.

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