Caring for CLL in Rural America

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Introduction

The epidemiology of CLL in the United States is unusual, with rates being unexpectedly higher in specific rural areas compared with the US average. While the cause of this is still being determined, it is clear that provision of guideline-recommended CLL care must be a priority in these at-risk populations. However, the delivery of CLL treatment in rural settings is fraught with challenges, and clinicians must learn to overcome barriers to CLL management that impede access to contemporary care and cutting-edge therapy. In this interview, Satish Shanbhag, MD, explores the challenges in delivering optimal CLL care in rural areas and strategies to mitigate these treatment barriers.

What is the epidemiology of CLL in rural America, and how is it different from other types of cancer?

To start, it is important to note that there is significant variability in the incidence of CLL within the United States.[1] Some of this variability can be explained by increased concentration of people with an ethnicity-related CLL risk; for example, the high rate of CLL in New York is related to the approximate 2 million Ashkenazi Jews residing in New York City, as this heritage is associated with increased risk for development of CLL. However, ethnicity does not explain the elevated CLL rates in more rural states such as North Dakota and Maine. North Dakota, which is one of the most rural states in the US, has one of the highest rates of CLL in the America (7 cases per 100,000 vs. the US average of 5 per 100,000).[1] What is even more perplexing is the fact that the incidence of CLL changes dramatically over a relatively small geographic area. From Fargo, North Dakota to Sioux Falls, South Dakota (a distance of less than 250 miles), the CLL incidence rate drops from 7 to 6 per 100,000. In adjacent Nebraska, the rate for CLL drops to 4.6 per 100,000. This represents a 40% difference in CLL rate in a day's drive.[1]

Although the reason for this phenomenon is not entirely clear, Dr. Schwartz and colleagues identified a correlation between age-adjusted CLL incidence rate and residential radon level.[2] The average radon level in homes in the US is about 1.3 picocuries per liter (pCi/L), but in Grand Forks, North Dakota, the average is 11.7 pCi/L, which is nearly 3 times the threshold (4 pCi/L) at which the EPA recommends remediation of homes. Radon is a particularly problematic carcinogen because it is colorless, odorless, and tasteless. This evidence, combined with data showing an increased risk for CLL among uranium miners and cleanup workers after the Chernobyl disaster, adds to the growing body of evidence suggesting that ionizing radiation may play a role in the etiology of CLL in these regions.

What are the challenges of diagnosing and treating CLL patients in rural areas?

Access to quality healthcare is dependent on many factors. Patients need 1) financial means to pay for services, 2) means to reach and use services (eg, transportation to services, the ability to take paid time off, etc.), 3) the ability to communicate with healthcare providers (eg, issues with fluency or health literacy), 4) trust that they can use services without compromising privacy, and 5) belief that they will receive quality care.[3] In general, rural populations experience lower access to healthcare in terms of affordability, proximity, and quality of care compared with suburban and urban populations.

Access to CLL care, specifically, is considerably impaired in rural areas because the population-to-hematologist/oncologist ratio is drastically lower than what is seen in urban or suburban areas. Many rural patients struggle with access to facilities and specialists who can diagnose CLL and implement appropriate intervention. Compared with urban settings, those in rural settings most likely will have to drive farther to see an oncologist. These individuals may even have to cross state lines to get to an oncologist who is qualified to treat CLL. This can be especially burdensome in the beginning of treatment when patients require intensive monitoring and frequent laboratory assessment. The need for frequent doctor visits and blood draws can be extremely challenging for patients who live in rural settings. Likewise, access to regular infusion services can be impeded due to geographic and logistic obstacles. Many patients must travel long distances to access infusion centers, placing an additional burden on these patients.

This challenge extends to subspecialty care as well. The treatment landscape of CLL has shifted considerably with the development of targeted therapies. While this change in practice has brought about a major improvement in treatment tolerability, there remain some side effects that we have not been able to completely mitigate. Treatment-related adverse effects such as cardiac toxicity, atrial fibrillation or arrhythmias of the heart, and gastrointestinal toxicities often necessitate sub-specialty care from cardiologists, gastroenterologists, and other non-oncology practitioners. Again, access to these types of healthcare professionals can be much more challenging in a rural area.

Other access issues are related to clinical trials. A substantial patient pool is necessary to run a viable research program, and these qualifications are often not met in rural areas. In fact, there is a recent movement towards the consolidation of cancer care, including CLL, into large urban cancer care centers; clinical trials often partner with these large centers to access their substantial CLL patient populations rather than coordinate with numerous, smaller, more rural centers. Penetration of research opportunities and access to novel therapeutics is therefore limited in rural settings. This can directly impact CLL outcomes. For example, the investigational drug pirtobrutinib (LOXO-305) was very recently found to overcome resistance to first- and second-generation Bruton tyrosine kinase (BTK) inhibitors.[4] Patients with this kind of resistance who live in rural areas may not be able to access clinical trials of this drug and will miss out on its potential benefits.

Finally, people in rural areas also tend to lack health insurance coverage. As of 2018, about 9% of rural populations have no health insurance, compared with 8.4% of those living within metropolitan areas.[3] In addition, average premiums are higher in rural counties compared with urban counties, and rural counties are more likely to have only a single insurer participating in the health insurance marketplace.[3] This amplifies healthcare access barriers and impacts overall outcomes. First, the tests that lead to a diagnosis of CLL can be expensive. Even the most basic test, flow cytometry, costs several hundred dollars. This can be difficult to afford for uninsured patients, especially in rural areas, where socioeconomic status is often lower as well. Lack of insurance coverage can therefore lead to diagnostic delays. Where insured, urban-residing patients may be diagnosed in the asymptomatic stage following routine bloodwork, patients with no health insurance and low access to healthcare may seek care only when they are sick (ie, symptomatic from advanced CLL).

These barriers greatly impact patient mortality. In general, rural cancer patients generally have poorer outcomes than urban- or suburban-dwelling individuals. Statistics published by the Centers for Disease Control and Prevention show that 180 people out of 100,000 die from cancer in rural areas compared with 158 out of 100,000 in urban areas. Evidence from clinical trials suggests that these differences are related to the care they receive (such as timely access to follow-up therapies) rather than individual patient factors.[5] Clearly, access to care plays a major role in CLL outcomes.

How do these challenges relate to novel CLL therapies?

The development of new drugs often translates into the need for new and/or different types of monitoring and follow-up. This is especially true for selectively targeting agents, such as ibrutinib, acalabrutinib, venetoclax, and PI3 kinase inhibitors, which have mostly replaced chemotherapy for both frontline and secondary treatment of CLL. For example, use of venetoclax requires rigorous monitoring for tumor lysis. Likewise, any of these novel agents can cause neutropenia during the first few months of use, as well as severe and fatal infections, requiring close monitoring for infectious complications.[6] This necessitates frequent patient visits and specialty laboratory access; two things which can be difficult in rural settings. Indeed, patients residing in rural areas often prioritize CLL treatments with a lower risk of adverse events due to their inability to easily access healthcare for such events.[7]

What tools and strategies can be used to overcome barriers to CLL care in rural areas?

While access to drugs continues to be a challenge for rural patients, the advent of specialty pharmacies that ship CLL drugs to the home has improved the ability for rural CLL patients to gain access to the drugs they need. While this option may be more challenging for very new or difficult-to-access drugs, many of the standard CLL agents can now be delivered in this manner.

Another advance in rural CLL care is telemedicine, which has increased by leaps and bounds since the COVID-19 pandemic. Provision of telemedicine is not only easier, eliminating the need for patients to drive long distances, it is also safer, especially in the midst of a pandemic. The use of telemedicine has been found to increase patient and clinical trial enrollment in rural communities.[8] Additionally, research has found that oncology telemedicine has demonstrated noninferiority to in-person care and high levels of patient and provider satisfaction.[9] I personally feel that a hybrid treatment strategy that involves virtual consults and follow-ups interspersed with in-person visits can reduce patient burden without negatively affecting the quality of care provided. However, the downside to telemedicine is the need for adequate internet access, which can be limited in rural areas. While regular phone calls can provide some information, video calls are really necessary for adequate communication and interaction. So these advances are far from perfect, and still are disproportionately challenging in rural settings.

Finally, healthcare professionals should always consider individual patient circumstances when selecting a treatment path. Patients with serious treatment access issues may consider therapies with infrequent dosing, less monitoring, and fewer adverse events to minimize healthcare visits. Patients who lack resources should also be provided with support services to overcome logistical, financial, and other treatment barriers. As with all patients, those with CLL in rural settings should receive personalized care that fits their goals, preferences, and abilities to ensure optimal treatment adherence and outcomes.

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